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TRANSMISSION OF INTRACRANIAL PRESSURE IN HYDROCEPHALUS IN INFANCY*

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Most of the studies on pressures within the craniovertebral cavity have been conducted on adult human beings or on full-grown animals. Obviously, the adult cranium and spinal column are relatively fixed in shape and in capacity and can probably be considered as a closed box completely filled with various soft or fluid substances to which the rules of physics concerning the transmission of pressure where fluids completely fill rigid, communicating containers will apply.

We do not propose to challenge the approximate accuracy of such a conception of transmission of pressure in adults, but we feel that the rigid box idea is unsound in theory and in fact frequently invalid in the human infant. In the first place, under every-day stresses the skull and the spinal column of the infant are subject to expansion, contraction and distortion to a degree which makes any such phrase as "closed box of constant volume" inapplicable. This is particularly evident in considering the mechanics of delivery of the fetus. Moreover, the physical characteristics of the intracranial contents in infancy have a distinct bearing on the question. The central nervous system itself is softer than in the adult; the falx and the tentorium do not, as in adults, arise entirely from rigid and fixed bony insertions which cannot be distorted. In the infant the bony attachments of the tentorium are relatively fixed, but the falx arises from a suture line and is in part supported only by the elastic tissue covering the fontanel. Clearly, the brain, so far as it is supported by the dural septums, is subject to measurable dislocation when the head is distorted. Under the various conditions which transiently raise pressure, the cranial capacity is instantly and palpably increased by bulging of the fontanel. Within a few days acute meningitis or other persistent causes of increased pressure will spread suture lines and even cause dislocation downward of the eyeballs as the orbital plates bend down.

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Far from having a fixed capacity, the infant's craniovertebral cavity is thus subject to marked changes in volume and its contents to easy movement. Under these circumstances we felt justified in reconsidering the experiments described by Leonard Hill in 1896, so far as they seem valid and pertinent. Hill's conclusions were that discontinuity of pressure could be brought about at the cleft of the tentorium or at the foramen magnum. On reading his work, it is obvious that by destroying the integrity of the skull he destroyed the "closed box" situation. It seems to us that his work, for the same reason that leads to valid criticism by workers with adult material, is more pertinent and interesting to pediatricians. We therefore became curious about relative pressures in infancy. At first we were interested in isolated manometric readings of spinal pressures in infants, but we were

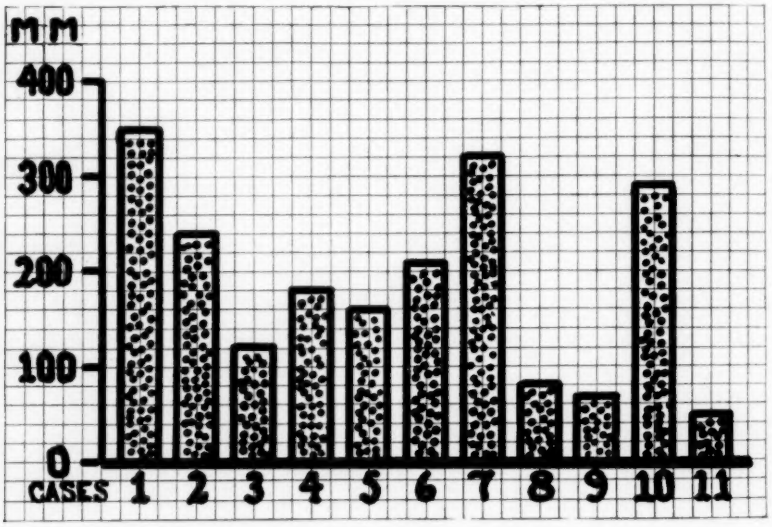

Fig. 1.—Spinal fluid pressures in millimeters of water in eleven successive cases of hydrocephalus.

impressed by the chaotic readings we obtained. The essential data regarding the cases studied are appended.

DATA OF CASES STUDIED

CASE 1.—V. C., aged 8 months, had hydrocephalus. The head was large at birth. An increase in size was noted at the age of 1½ months, and continued. The pressure reading on April 4, 1927, was 350 mm. Seventy-five cubic centimeters of fluid was withdrawn following tap. The thickness of the skin plus the cortex was ¼ inch (6.35 mm.)

CASE 2.—H. M., aged 3 months, had marked hydrocephalus which developed after birth. The pressure was 120 mm. of water. The thickness of the skin plus the cortex was ¼ inch (6.35 mm.)

CASE 3.—J. K. had hydrocephalus from birth. Lumbar puncture was performed because of a full anterior fontanel. The pressure was 240 mm. The thickness of the skin plus the cortex was ½ inch (12 cm.)

CASE 4.—L. H., aged 14 months, had hydrocephalus at birth, which was gradually increasing. The pressure was 180 mm. The thickness of the skin plus the cortex was 1/16 inch (1.5 cm.)

CASE 5.—B. J., delivered by cesarean section, had hydrocephalus at birth. The pressure on the third day was 160 mm.

CASE 6.—This patient had syphilitic meningitis. The pressure was 210 mm.

CASE 7.—J. B., aged 17 months, had a condition of hydrocephalus, noted at birth. The pressure was 320 mm.

CASE 8.—S. W., aged 7 to 8 weeks, had hydrocephalus at birth. The pressure was 80 mm. The thickness of the skin plus the cortex was 3/16 inch.

CASE 9.—K., aged 4 weeks, had hydrocephalus which was not present at birth, but gradually developed after birth. The pressure was 70 mm.

CASE 10.—C. P., aged 3 months, presented a development of hydrocephalus after birth (between the ages of 6 weeks and 3 months). It was of the communicating type. Five days following lumbar puncture, the temperature rose. Lumbar puncture revealed cloudy fluid, 600 cells mostly lymphocytes, and no organisms. The patient was treated with antimeningococcic serum, and improved. The assumption is that manipulation resulted in the breaking down of a meningococcus abscess. The pressure was 290 mm.

CASE 11.—K., aged 11 months, had meningococcus meningitis. On the twentieth day of disease, the lumbar pressure was 50 mm.

In the majority of cases in early childhood in which crying and restlessness are noted, unpredictable variations seem to be inevitable and unreliable. There are of course exceptions, notably in cases of coma or of infants in whom responses have been decreased because of birth injury. Furthermore, the spinal pressure in infants is not necessarily equal to subtentorial or supratentorial pressure. In many cases, simultaneous ocular observation of two manometers—one connected with a needle in the spinal canal and one with a needle in the ventricle—will apparently show a simultaneous rise and fall of fluid. On the other hand, such apparently simultaneous variations are by no means always present. It should be realized, of course, that all degrees of block in transmission of pressure were recognized and studied under pathologic conditions. More or less casually, delay in transmission was noted. Most of these observations were made on adults.

If the conception of an elastic craniovertebral cavity in the infant and the idea that its more solid contents are loosely held in position are correct, certain definite phenomena are to be expected. If pressure is rapidly increased in the supertentorial chamber, which of course is by far the most easily expansible, it is reasonable to suppose that part of the rise will be noted only in that chamber, and that it will be both delayed in time and decreased in volume as the displaced fluid flows through the narrow channels of the aqueduct and the foramina. The

degree of delay and of decrement will depend on the size of the communicating channels.

In considering infants with hydrocephalus, it is evident that some of them have enormously dilated channels between the ventricles and the spinal subarachnoid space, some relatively normal channels and some none at all. Ocular observation alone is not always convincing so far as time relations in the propagation of pressure is concerned.

For this reason, while studying spinal fluid pressure in hydrocephalic infants we felt that some information of value might be obtained were it possible to chart with some accuracy simultaneous pressure responses in the intracranial vault and in the spinal canal. The accompanying

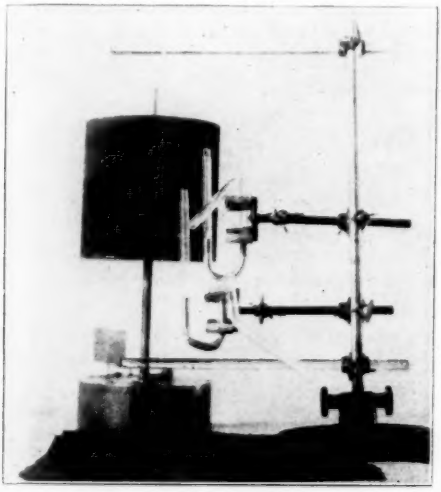

Fig. 2.—Arrangement of manometers recording simultaneous ventricular and spinal pressures.

graphic pressure records were obtained with the use of mercury manometers, connected by glass, saline-filled tubing with connections of thick-walled rubber tubing. The apparatus is easily set up, but it is technically rather difficult, without the use of anesthesia, to get continuous records.

Every effort was made to eliminate loss of fluid. Pressure was imposed by the simple process of compressing the vault of the infant's cranium between the hands. This procedure obviously vitiated the "rigid container" conception. The results, although clearly lacking any authority due to numerical adequacy, seem to us suggestive. Three types of response were seen.

1. No propagation of pressure occurred. In this case, tumor was responsible, as confirmed by autopsy.

2. The propagation of pressure was apparently immediate and without decrement. In this case, we assumed that there was a series of wide channels.

3. Propagation of pressure was subject to some delay and to slight decrement. As we were particularly interested in this aspect

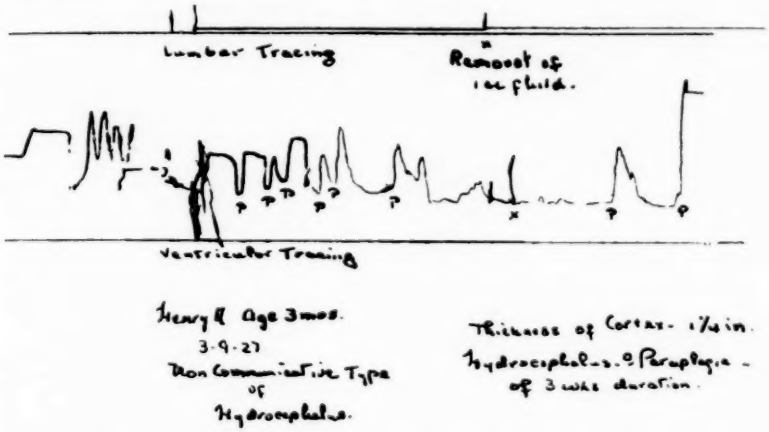

Fig. 3.—Noncommunicating hydrocephalus due to tumor.

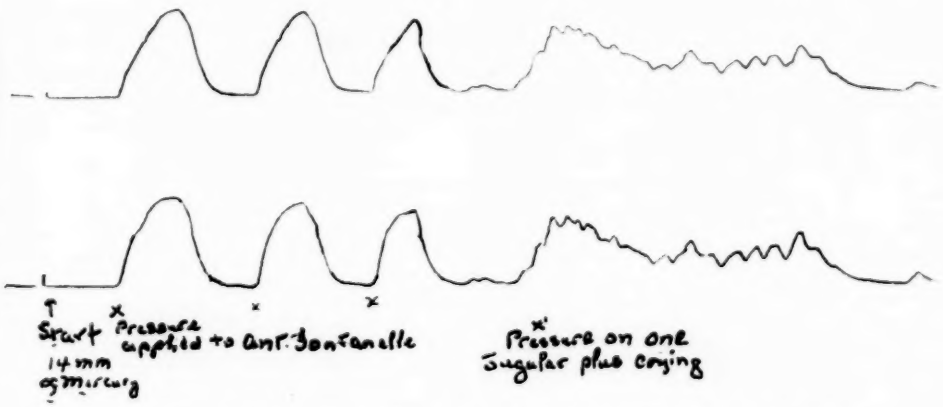

Fig. 4 (case 8.)—Communicating hydrocephalus with no delay or decrement; upper tracing, ventricular; lower tracing, spinal.

of pressure transmission we present, in addition to the tracing which is retouched for clearness in reproduction, a curve which is corrected by accurate calibration of the entire apparatus. This curve, marked II in figure 6, is compared to that in figure 3 which is shown as I.

CONCLUSIONS

In infants, the contents of the craniovertebral cavity do not transmit pressure according to the laws governing the pressure relations where fluids completely fill rigid containers.

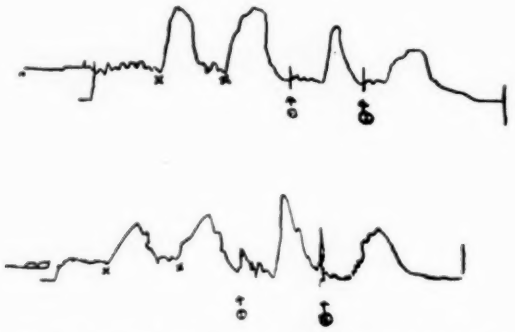

Fig. 5 (case 3).—Communicating hydrocephalus with delay and decrement; upper tracing, ventricular; lower tracing, spinal.

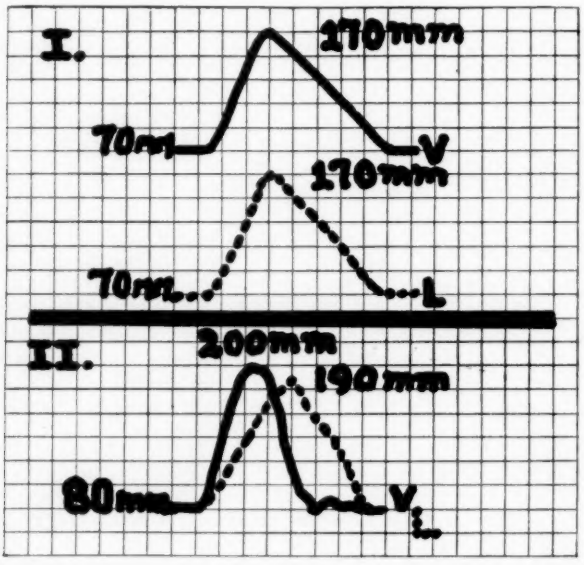

Fig. 6.—Spinal fluid pressures in hydrocephalus; I indicates free communication without delay or decrement; II, communication, but with delay and decrement.

1. In hydrocephalus, the propagation of abruptly applied pressure of short duration from ventricle to spinal space may be essentially immediate and without decrement. In this case, we assume the probability of widened channels between the two cavities.

2. Delay in time and decrement in intensity may be noted. This suggests patent though narrow channels. Though we do not have evidence on this point, we suggest that this delay and decrement may also occur in normal infants.

3. The propagation of pressure may be completely blocked. This means, of course, that at the time of reading, at least, a complete discontinuity of pressure exists.

In general, we believe that the time element in the propagation of pressure is interesting, that it can be graphically recorded, and that it is possible that it may be made clinically useful. Certainly, the reliance on isolated measurements of spinal fluid pressure, as indicating intracranial pressures, seems likely to lead to serious error, and the application of the "closed box" theory to infants seems to us entirely unsound.

THE DEMONSTRATION OF TUBERCLE BACILLI IN SMALL CHILDREN WITH PULMONARY TUBERCULOSIS *

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It is difficult to demonstrate the presence of tubercle bacilli in pulmonary tuberculosis in children who are so small that they swallow the expectoration. Positive results are rarely obtained when attempts are made to secure some suitable clots of the expectoration by means of a cotton swab. Thus, the report presented by one of us before the congress in Helsingfors, in 1927, on sixty-two cases of pulmonary tuberculosis in children less than 3 years old did not include a single instance of the successful demonstration of tubercle bacilli by this method.

In 1898, Meunier [1] recommended lavage of the stomach of children during fasting, centrifugation of the water and search for bacilli in the sediment. This method, however, was never employed extensively. In 1927, however, Armand-Delille and Vibert [2] reported their results with Meunier's method, which they had improved by homogenizing the sediment before staining it after Ziehl-Neelsen's method. They were able to demonstrate the presence of tubercle bacilli in 31 per cent of 110 cases, and their results were so satisfactory that we tried the method on our patients.

We proceeded in the following manner: In the morning—after the child had fasted at least six hours—the stomach was washed with from 200 to 300 cc. of sterile water; the wash-water was centrifugated; the sediment was homogenized, stained after Ziehl-Neelsen's method and examined. We did not restrict ourselves, however, to the microscopic examination alone; in addition we made cultures from the sediment on Petroff's medium and inoculated guinea-pigs with the sediment.

In this way we examined the gastric lavage from fifteen patients, who may properly be divided into three groups.

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* From the Children's Hospital "Fuglebakken" and the State Serum Institute.

1. Meunier, Presse méd. **2**:81 (Aug. 13) 1898.

2. Armand-Delille, P. F., and Vibert, J.: Presse méd. **26**:402, 1927. Armand-Delille, P. F.: Pulmonary Tuberculosis in Infants, Am. J. Dis. Child. **34**:547 (Oct.) 1927.

The first group comprised six children, one of whom was 2 years old and the other five, from 7 to 10 months. Five of the children had been exposed to infection at home, while no such information was obtained in the sixth case. All the children gave positive tuberculin reactions, and all presented stethoscopic signs of changes in the lungs—infiltrations and râles. One child was too sick for roentgen examination. In the other five cases, the x-ray plates showed more or less extensive processes of infiltration in the lungs. The child aged 2 years is living and improving; the other five have died. Microscopic examination of the sediment showed tubercle bacilli in four cases. Culture on Petroff's medium produced tubercle bacilli in all six cases. Inoculation of the sediment from five children into guinea-pigs produced tuberculous lesions, while that from the sixth child caused death a few days after inoculation into the animal.

In the six children the diagnosis of pulmonary tuberculosis could be made with almost absolute certainty, even without the demonstration of bacilli. Here the bacillary observations are of lesser importance, although in the nature of things, there is always a certain satisfaction to be able to make an incontestable diagnosis. The observation of bacilli is of greater interest only in the case of the 2 year old boy who is still living; in this case, we consider the changes in the lungs that can be made out on auscultation and on roentgen examination to be epituberculous. If this view proves to be correct—which only the further course of the lesion can decide—we are dealing with epituberculosis in a child who also has an open pulmonary tuberculosis. Such cases have been observed before, but they are not in keeping with Eliasberg and Neuland's definition of epituberculosis.

The second group comprised five children, one being 1 year old, the others from 5 to 8 months. Four of these children were exposed to infection at home; in the fifth case, that of an adopted child, nothing was known with regard to the source of infection. All five children gave a positive tuberculin reaction; in none of them could pulmonary changes be determined on auscultation. Roentgen examination, on the other hand, revealed infiltrations in the lungs in all five cases, although these processes were less pronounced in this group—in four of the cases, at any rate—than they were in the first group. These children are steadily improving, with exception of the patient with marked roentgenoscopic changes who also suffered from tuberculous peritonitis and tuberculosis of the joints. In only one of these cases could tubercle bacilli be demonstrated under the microscope; but cultivation on Petroff's medium gave growth in four cases, and guinea-pigs inoculated with the sediment showed tuberculous lesions on autopsy in all five instances.

In this group the observation of bacilli has been valuable information. Auscultation of the lungs did not reveal any changes, and the diagnosis of pulmonary tuberculosis could hardly be made, in four cases at least, on the basis of the roentgen observations alone.

To avoid any misconception, we may add that none of these eleven children showed any tuberculous ulceration on the tonsils or anywhere in the fauces.

The third group comprised four patients, from 1 to 8 years old. One of these presented a family history of consumptive parents; nothing is known of the source of infection in the other three cases. All four gave a positive tuberculin reaction. Physical examination showed normal conditions in three of them, and roentgen examination did not show any sign of infiltration in the lungs of these patients. On the other hand, in the fourth case, that of a girl, aged 2 years, whose parents both suffered from pulmonary tuberculosis, auscultation as well as roentgen examination showed definite signs of infiltration in the right lung. As this patient also presented symptoms of active tuberculosis—fever and anemia—it was expected that examination of the contents of the stomach would show the presence of tubercle bacilli, but every test—the microscopic examination as well as the cultures and the animal inoculations—gave negative results, although the tests were repeated three times.

In the other three cases, the examinations were likewise carried out in four series of tests. They all gave negative results, an outcome that had also seemed most likely beforehand.

Material that covers only fifteen cases is naturally too small to warrant any general conclusions, but it appears as if this method is efficient for demonstrating bacilli in cases in which success is rarely obtained by other methods.

By this method, one is able to make the diagnosis of open pulmonary tuberculosis in cases in which this would not be possible by ordinary methods—a fact that is of the greatest importance to therapy as well as to prognosis.

The demonstration of bacilli bears out the view that infants with pulmonary tuberculosis are infective, and consequently ought to be kept strictly isolated from other nonconsumptive children; further, that the nurses should be instructed in taking care to avoid infection as far as possible.

The demonstration of bacilli is also of considerable importance in that it furnishes the means of collecting incontestably positive cases of pulmonary tuberculosis; when there is a sufficiently large number of such cases, some light will be thrown on the prognosis and on the value of the therapy in the various cases.

The drawbacks of the method are limited to that part of the work that is done in the laboratory. This work is time-consuming as well as expensive, and the results from incubation on Petroff's medium and animal experimentation do not appear in less than from four to six weeks. It is not enough merely to homogenize the sediment and examine it under the microscope. Considering only those eleven children in whom bacilli were demonstrated, twenty-seven microscopic examinations were made in these cases, and only five resulted in positive observations; in other words, if a microscopic examination had been the only test employed, tubercle bacilli would have been demonstrated in only five of the eleven children. By the additional cultivation on Petroff's medium—nine of seventeen gave growth of tubercle bacilli, one failed—the number of bacillus-eliminating cases rose from five to ten of the eleven cases. The presence of tubercle bacilli in the eleventh case was demonstrated only by animal experimentation, in which nineteen gave positive results, five negative and three failed.

Consequently, when microscopic examination fails to show the presence of tubercle bacilli, one should make cultures of the sediment on Petroff's substrate and inoculate guinea-pigs with the sediment.

REPORT OF CASES

Group I.—Case 1.—Ib. R., aged 2 years, was admitted to the hospital on Jan. 28, 1928. The patient had always been disposed to bronchitis. There had been a rise in temperature for the last five days. The fauces were hyperemic on admission. A slight cough was present, which subsided rapidly. The mother had pulmonary tuberculosis.

There was some rise of temperature on admission; it was normal after two weeks, but became subnormal shortly thereafter. Later it was subnormal most of the time. The last month it had been normal, except for a febrile period during an attack of angina.

There was a dulness over the upper part of the right lung on the anterior and posterior surfaces. There were bronchial respirations below the right clavicle. Râles were not present. There was no particular change in the observations on all subsequent examinations.

On roentgen examination an area of dense infiltration was found in the upper lobe of the right lung; a few spots were seen below this area. There were no changes on subsequent examinations. The Pirquet and Moro reactions were positive.

On February 7, direct microscopic examination of the sediment from the stomach lavage revealed *Bacillus tuberculosis.* The culture on Petroff's medium produced a growth of *B. tuberculosis.* Inoculation into a guinea-pig produced tuberculosis. On February 13 and 16, the same results were obtained.

Case 2.—Gregers G., aged 9 months, was admitted to the hospital on Jan. 31, 1928, with an illness that began four weeks before the time of admittance with fever. The paternal and the maternal aunt suffered from tuberculosis, and both visited the home frequently. Fever was present during the stay in the hospital.

There was a dulness over the apex of the right lung, anteriorly and posteriorly, with impaired respiration. Râles were present in the rest of the right lung and in the left axilla. On roentgen examination, one larger area of infiltration was seen in the upper lobe of the right lung; there were numerous small spots in both lungs (miliary dissemination). The Pirquet and Moro reactions were positive.

On February 11, by direct microscopic examination, sediment from the stomach lavage revealed 1 acid-fast and alcohol-fast bacillus. Culture on Petroff's medium produced a growth of *B. tuberculosis*, and inoculation into a guinea-pig produced tuberculosis. On February 21, direct mircroscopic examination revealed *B. tuberculosis*. Culture on Petroff's medium showed a growth of *B. tuberculosis*, and inoculation into a guinea-pig produced tuberculosis.

The patient grew worse steadily, and died on March 18.

Case 3.—Lis M., aged 8 months, was admitted to the hospital on Jan. 26, 1928. The father suffered from pulmonary tuberculosis. The patient had high fever throughout the stay in the hospital.

There was a dulness over the entire anterior surface of the right lung, with crepitation and dry crackling râles. There was dulness over the left anterior surface to the third costal rib; râles were present at the base of the left lung anteriorly and in the left axilla. On roentgen examination both lungs were found to be filled with closely packed infiltrations of practically the same size throughout. The diagnosis was miliary tuberculosis. The Pirquet and Moro reactions were positive.

On February 16, direct examination of the sediment from the stomach lavage revealed *B. tuberculosis*. Culture on Petroff's medium showed a growth of *B. tuberculosis*. Inoculation into a guinea-pig produced tuberculosis. On February 25, the same results were obtained.

The patient returned to her home on March 8; later her death was reported.

Case 4.—Ib E., aged 8 months, was admitted to the hospital on Feb. 2, 1928. His father suffered from pulmonary tuberculosis.

He had had fever for six weeks. He coughed a good deal, with croupous sound. Fever was present during the entire stay in the hospital, except during the last days before death.

There was dulness over both apexes; bronchial respirations and râles were heard over the upper part of the posterior surface of the right lung. On roentgen examination, a marked shadow was seen over the upper third of the right lung; the upper two thirds of the left lung were markedly spotted and darkened. Subsequent examination showed these changes to have extended considerably. The Pirquet and Moro reactions were positive.

On February 7, direct examination of the sediment from the stomach lavage revealed a few *B. tuberculosis*. A culture on Petroff's medium produced a growth of *B. tuberculosis*. A guinea-pig died a few days after inoculation.

Case 5.—Ruth I., aged 10 months, was admitted to the hospital on Dec. 28, 1927. The mother's father had died of pulmonary tuberculosis five years previously. The mother looked miserable. The patient was well until from two to three months previously, at which time she began to cough. She had been losing weight since. The temperature had been elevated for some time. There was a continuous fever while she was in the hospital.

A dulness was present over both supraspinous areas. There were scattered coarse, moist râles in the left infrascapular space. At a subsequent examination, the dulness extended from the apex to the base of the left side, anteriorly and posteriorly; there was dulness over the upper half of the anterior surface of the right lung and over most of the posterior surface. Bronchial respiration was present in some areas, and moist râles were found. On roentgen examination, cloudiness

was present, with numerous infiltrations of the entire right and upper two thirds of the field of the left lung. The upper portion of the median shadow was extraordinarily wide (lymph glands or enlarged thymus). The Pirquet reaction was positive; the Moro reaction was negative.

On Jan. 1, 1928, direct examination of the sediment from the stomach lavage revealed *B. tuberculosis*. A culture on Petroff's medium showed a growth of *B. tuberculosis*. There were no signs of tuberculosis four weeks after inoculation into a guinea-pig. On January 27, direct examination revealed *B. tuberculosis*. Culture on Petroff's medium showed a growth of the bacillus, and inoculation into a guinea-pig produced tuberculosis.

The patient died on Feb. 16, 1928.

CASE 6.—Knud N., aged 7 months, was admitted to the hospital on May 22, 1928. The father had had tuberculosis as a child, but was well at the time the patient came to the hospital. His family had a tendency toward tuberculosis; a sister had died of tuberculous meningitis two weeks previously. The mother's sister suffered from active pulmonary tuberculosis; she had been a frequent visitor at the home. The patient had influenza three weeks before admission; from that time there was high fever and progressive weakness. Fever was present during the entire stay in the hospital. A roentgen examination was not made. A pneumonic process was found in both lungs. The Pirquet and Moro reactions were positive.

On June 6, direct examination of the sediment from the stomach lavage revealed *B. tuberculosis*. A culture on Petroff's medium showed a growth of *B. tuberculosis*, and inoculation into a guinea-pig produced tuberculosis. On June 19, the same results were obtained.

The patient died on July 11.

Group II.—CASE 7.—Inger H., aged 1 year, was admitted to the hospital on July 12, 1928. An uncle was said to have pulmonary tuberculosis; a brother died from "galloping pneumonia." The patient had coughed for the six months preceding admission. Diarrhea had begun two weeks previously. Fever was present at the time of admission. Later (after a few days), the patient was subfebrile and had occasional days of normal temperature.

On roentgen examination, a diffuse shadow was found over the apex of the right lung, and some spotted, mottled clouding of the entire right lung was present. There was a marbled spotting in the upper one third of the left lung. The hilum shadows were somewhat enlarged on both sides. There was a dulness below the right clavicle and over the lower surface of the right lung posteriorly, at which place râles were heard occasionally. The abdomen was extremely large and distended. There was no sign of ascites.

On July 16, direct examination of the sediment from the stomach lavage showed *B. tuberculosis*. A culture on Petroff's medium showed a growth of *B. tuberculosis*. Inoculation into a guinea-pig produced tuberculosis. On July 23, direct examination revealed 1 acid-fast and alcohol-fast bacillus. A culture on Petroff's medium showed a growth of *B. tuberculosis*, and inoculation into a guinea-pig produced tuberculosis.

CASE 8.—Johanne M., aged 8 months, was admitted to the hospital on April 19, 1928, with a fetid discharge from the left ear. There was no cough worth mentioning. Information could not be obtained as to the source of the infection. The patient was febrile on admission; she soon became subfebrile, which condition persisted for about three weeks; then the temperature became normal.

Abnormal observations were not found at any time on auscultation. On roentgen examination dimness of the upper half of the right lung was seen.

Numerous infiltrations the size of a pinhead were found in both lungs. The Pirquet and Moro reactions were positive. Tuberculids were present on the left cheek and on the lower part of the right arm.

On April 24, direct examination of the sediment from the stomach lavage revealed *B. tuberculosis*. A culture on Petroff's medium showed a growth of *B. tuberculosis*. Inoculation into a guinea-pig produced tuberculosis. On May 14, direct examination revealed *B. tuberculosis*. A culture on Petroff's medium showed a mixed growth. The guinea-pig died shortly after being inoculated. On June 9, the results were the same as those after examination on April 24.

CASE 9.—Holger N., aged 6 months, was admitted to the hospital on March 17, 1928. He had been in Rigshospital three months for diarrhea, and immediately afterward in a clinic for children for one month. He was discharged from the latter ten days before admission to the Children's Hospital. The previous diagnosis was said to have been bronchitis. He had always had some cold, a cough and a little fever; he sweat both during the day and at night; he had lost 1.5 Kg. He was discharged from the hospital on July 26. The father suffered from pulmonary tuberculosis. The patient was small, emaciated and pale, but was bright and active. He was subfebrile for the first six weeks; his temperature was not above 38 C. (100.4 F.). Later the temperature was normal.

Auscultation did not reveal definite abnormality. On roentgen examination many minute spots were found in both sides of the chest, mostly in the hilar regions. The Pirquet and Moro reactons were positive.

On April 12, direct examination of the sediment from the stomach lavage revealed *B. tuberculosis*. A culture on Petroff's medium showed a growth of *B. tuberculosis*, and inoculation into a guinea-pig produced tuberculosis. On April 26, the same results were obtained. On May 3, direct examination revealed *B. tuberculosis*. A culture on Petroff's medium showed a growth of *B. tuberculosis*. Inoculation into a guinea-pig did not produce tuberculosis. On June 8, the guinea-pig died twenty-four hours after receiving the inoculation.

CASE 10.—Lillian L., aged 5 months, was admitted to the hospital on May 31, 1928. The illness was of two weeks' duration. The mother had died of pulmonary tuberculosis. A high fever was present at the time of admission; three weeks later the temperature was normal, and remained normal the following two weeks, at which time subfebrile temperature occurred in connection with angina.

At the time of admission, harsh respiration was heard in the right axilla and in the lower part of the posterior surface of the right lung, together with a few râles; dulness was not present. No abnormality was noted on subsequent examinations. On roentgen examination a hilum shadow on the left side was somewhat enlarged and rather dense. The upper portion of the median shadow was somewhat irregular and apparently enlarged. There were several small infiltrations upward and medially in the fields of both lungs. The Pirquet and Moro reactions were positive.

On June 7, direct examination of the sediment from the stomach lavage showed *B. tuberculosis*. A culture on Petroff's medium showed a growth of *B. tuberculosis*. Inoculation into a guinea-pig did not produce tuberculosis. On June 21, direct examination revealed *B. tuberculosis*. A culture on Petroff's medium showed a growth of *B. tuberculosis*, and inoculation into a guinea-pig also produced tuberculosis. On August 1, the same results were obtained as on June 7.

The patient was discharged from the hospital on September 22.

CASE 11.—Nigilla L., aged 7 months, was admitted to the hospital on March 9, 1928. The mother was in the hospital because of tuberculosis. The patient was transferred from the surgical department—where bilateral mastoidotomy had been

performed—on account of malnutrition. There were periods of fever at first; later there was an almost constantly subfebrile temperature.

There was a sharp tone over the upper portion of the posterior surface of the right lung. No other abnormality was discovered at any time. On roentgen examination several scattered infiltrations were found in both lungs, and there was a larger area of intense obscurity upward and medially in the field of the right lung. The Pirquet and Moro reactions were positive.

On March 13, direct examination of the sediment from the stomach lavage showed *B. tuberculosis*. A culture on Petroff's medium showed a growth of *B. tuberculosis*, and inoculation into a guinea-pig produced tuberculosis. On June 14 and July 31, the same results were obtained.

The patient was discharged from the hospital on September 27.

Group III.—Case 12.—Jørgen R., aged 8 years, was admitted to the hospital on Feb. 11, 1928. There was no instance of tuberculosis in the family. The temperature was normal during the whole stay in the hospital. Auscultation did not reveal abnormality. On roentgen examination, numerous shadows of individual lymph glands were seen in both hilar regions, particularly on the right side; infiltrations were noted on the left side, in a medial region below the clavicula; on the right side, a zone of infiltration was present, around the hilum shadow. The Pirquet and Moro reactions were positive.

On March 29, direct examination of the sediment from the stomach lavage revealed *B. tuberculosis*. A culture on Petroff's medium showed a growth of *B. tuberculosis*. Inoculation into a guinea-pig did not produce tuberculosis.

The patient was discharged from the hospital on March 10, 1928.

Case 13.—Kirsten C., aged 2 years, was admitted to the hospital on Feb. 1, 1928. There had not been a case of tuberculosis in the family. The patient had never thrived well. The appetite had been poor for the past three weeks. It was noted that the abdomen was increased in size. A cough was not present. The temperature was febrile or subfebrile throughout her stay in the hospital.

Auscultation did not reveal an abnormality. The abdomen was extremely large, the circumference being 47 cm. Ascites were present. Just above the umbilicus an oblong, transverse, somewhat nodular, firm and not tender intumescence was felt. On roentgen examination, an abnormality was not demonstrated in either the chest or the abdomen. The Pirquet and Moro reactions were positive.

On February 21, direct examination of the sediment from the stomach lavage revealed *B. tuberculosis*. A culture on Petroff's medium showed a growth of *B. tuberculosis*. Inoculation into a guinea-pig did not produce tuberculosis.

The patient was discharged from the hospital on March 10.

Case 14.—Thorkild Petersen was admitted to the hospital on Aug. 1, 1927. The diagnosis was: rachitis and bronchitis; he was observed for tussis convulsiva. The Pirquet and Moro reactions were negative. He was discharged on August 17.

The patient was readmitted to the hospital on June 14 because of rachitis. Particular information was not obtainable. There was no instance of tuberculosis in the family. There was no abnormality except rachitis. The temperature was subfebrile the first six weeks the patient was in the hospital. Auscultation did not reveal any abnormalities. On roentgen examination there appeared to be a slight infiltration around the left hilum. No other abnormality was noted. The Pirquet and Moro reactions were positive. On August 20, direct examination of the sediment from the stomach lavage revealed *B. tuberculosis*. A culture on Petroff's medium showed a growth of *B. tuberculosis*. Inoculation into a guinea-pig did not produce tuberculosis. On July 12, the same results were obtained.

CASE 15.—Lizzie H., aged 2 years, was admitted to the hospital on Feb. 25, 1928. Both parents suffered from pulmonary tuberculosis. The temperature was frequently elevated.

There was dulness over the lower two thirds of the right lung, anteriorly and posteriorly. Bronchial respirations were present; fine as well as coarse râles were heard. The dulness and respiratory changes were somewhat diminished while the patient stayed in the hospital, but many râles were frequently heard in both lungs. On March 7, roentgen examination revealed markedly spotted, large, dense hilum shadows on the right side. There were several small spots around the left hilum shadows. On September 5, there were considerable infiltration processes in both lungs, particularly in the medial portion of the right side. The Pirquet and Moro reactions were positive.

On March 5, direct examination of the sediment from the stomach lavage revealed *B. tuberculosis*. A culture on Petroff's medium showed a growth of *B. tuberculosis*. Inoculation into a guinea-pig did not produce tuberculosis. On March 23 and April 19, the same results were obtained.

The patient was discharged on May 19.

THE PROGNOSIS OF TUBERCULOSIS IN INFANTS

A FOLLOW-UP STUDY OF FOUR HUNDRED AND FOUR TUBERCULOUS INFANTS FOR A PERIOD OF FROM ONE TO EIGHT YEARS *

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The purpose of this work was to ascertain the fate of the infants who had been infected with tuberculosis during the first two to two and a half years of life. Until recently, the generally accepted opinion was that the presence of a tuberculous lesion in the infant's organism or even the presence of a positive tuberculin reaction without any demonstrable lesion was practically synonymous with death. Modern textbooks on pediatrics still express this view. Holt,[1] in "Diseases of Infancy and Childhood," wrote: "Under one year a positive reaction (tuberculin) usually indicates an active tuberculous process. Many have taken the ground that an infant under one year with a positive reaction is doomed. We do not believe the outlook quite so hopeless; but such a reaction is certainly of serious import." Porter and Carter,[2] in their book, "Management of the Sick Infant," wrote: "Recovery from the disease when it attacks the child during the first year is most unusual." William Funkhauser and R. G. McAliby [3] in "Clinical Pediatrics" stated, "Under 1 year of age a positive tuberculin test is pathognomonic of active tuberculosis. Infants have very little, if any, resistance; no immunity has been developed . . . but while the vast majority of infected infants are lost, a few cases have been reported as having overcome the infection and regained good health." L. W. Sauer [4] in Abt's "Pediatrics" quoted Comby as saying, "Tuberculosis in infants is very grave, but not invariably fatal." Feer [5] stated, "During the first three years, a positive reaction is a very serious affair—at this time most cases of tuberculosis

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* From Professor Clemens Pirquet's Children's Hospital of Vienna.

1. Holt, L. E., and Howland, G.: The Diseases of Infancy and Childhood, New York, D. Appleton & Company, 1926, p. 914.

2. Porter and Carter: Management of the Sick Infant, St. Louis, C. V. Mosby Company, 1927, p. 441.

3. Funkhauser, William; and McAliby, R. G., in Clinical Pediatrics, New York, D. Appleton & Company, 1927, vol. 60, p. 231.

4. Sauer, L. W., in Abt, I. A.: Pediatrics, Philadelphia, W. B. Saunders Company, 1924, vol. 5, p. 602.

5. Feer, E.: The Diagnosis of Children's Diseases, Philadelphia, J. B. Lippincott Company, 1925, p. 523.

are active." Griffith and Mitchell [6] wrote: "In the first year there appears to be very little power of resistance, the disorder assumes an active form from the beginning, and the great majority of those infected die. Yet certain investigations, as by Pollak, Oswald and others, indicate that the prognosis is not so absolutely bad as has been generally believed." Morse [7] expressed the most optimistic view: "Contrary to the general belief of a few years ago, a positive tuberculin test does not by any means condemn a baby to death—while tuberculosis in infancy which gives definite physical signs carries a grave prognosis, it is not, as we used to think, invariably fatal. Babies with recognizable tuberculosis not infrequently recover." Finkelstein [8] said: "A number of children who had contracted tuberculosis, in the first year of life, even in the first six months of life, have been followed up for 3, 4, or more years and have been found to be in good physical condition." Kleinschmidt [9] stated: "The mortality of tuberculosis in infants is very high. Tuberculous infection, not only tuberculous activity, should be looked upon with apprehension."

When the medical literature is reviewed, one finds somewhat more optimistic views than those expressed in the textbooks. In 1912, Hamburger [10] found that 80 per cent of the infants infected before they were 1 year old died, while only 10 per cent of those infected during the second year died. In the same year, Hahn [11] studied sixty-nine infants, and his results were given as follows: Seventeen per cent who were under 12 months of age recovered, as did 26 per cent who were infected between 6 and 16 months of age, and 39 per cent who were infected between the ages of 12 and 24 months. At about the same time, Pollak [12] reported that among twenty-one infants infected during the first six months of life the mortality was 85.7 per cent, and that among forty-six infected during the second half of their first year it was 58.7 per cent. In 1913, Brown [13] reported a mortality of 70 per cent among 114 children under 2 years of age who showed a positive skin

6. Griffith and Mitchell: The Diseases of Infants and Children, Philadelphia, W. B. Saunders Company, 1927, vol. 1, p. 649.

7. Morse: Clinical Pediatrics, Philadelphia, W. B. Saunders Company, 1926, p. 340.

8. Finkelstein, H.: Lehrbuch der Säuglingskrankheiten, Berlin, Julius Springer, 1924, p. 464.

9. Kleinschmidt: Tuberkulose der Kinder, Leipzig, J. A. Burth, 1927, p. 132.

10. Hamburger, F.: Die Tuberkulose des Kindersalters, Vienna, Julius Springer, 1912.

11. Hahn: Monatschr. f. Kinderh. **10**:531, 1912.

12. Pollak: Beitr. z. klin. d. Tuberk. **19**:373, 1911.

13. Brown: Arch. Pediat. **30**:665 (Sept.) 1913.

reaction. In 1921, Dunn and Cohen [14] reported a mortality of 53 per cent in children under 2 years, and in 1922, Oswald [15] found a mortality of 59.4 per cent. Van Dam-Stokkink,[16] Davis,[17] Reuben and Smith,[18] Lemaire [19] and Lozano [20] found the following mortalities, respectively, 87, 44, 68, 24 and 12 per cent. Nassau and Zweig [21] found that all of their twenty children infected during the first three months of life died; of sixteen children infected during the second quarter, only two remained alive; of ten infected during the third quarter, seven were alive, and of three infected during the last quarter of the first year, one died. More recently, Wahlquist and Myers [22] found that of seventy-one tuberculous children under 2 years of age, only six died, a mortality of 8.4 per cent.

In 1927, Langer [23] reported seventeen cases of healed tuberculosis in infants, six of whom had been infected during the first quarter of the first year of life. Asserson [24] reported that among 207 infants with a positive tuberculin reaction there was a mortality rate of 38.6 per cent; among sixty-one infants with tuberculosis of the hilum the mortality was 21.3 per cent, and of twenty-five infants with chronic tuberculosis, 32 per cent died. Recently, Mandl [25] reported a mortality of 47.72 per cent among forty-four tuberculous infants.

These variations in the mortality rates as reported by the various writers are undoubtedly due, in large measure, to the type of tuberculosis and to the condition of the patients when they were first seen. The older ideas were based chiefly on observations at autopsy or on advanced, generalized forms of tuberculosis. Today, with the more common employment of the tuberculin test and roentgenologic examinations, the diagnosis of tuberculosis can be made at an early stage, and the mortality rate then becomes much lower. A true conception of the fate of tuberculous infants cannot be gained from a study of patients in hospitals only or from a study of far advanced cases of tuberculosis.

14. Dunn, C. H., and Cohen, S. A.: Diagnosis and Prognosis of Tuberculosis, Am. J. Dis. Child. **21**:187 (Feb.) 1921.
15. Oswald: Monatschr. f. Kinderh. **23**:168, 1922.
16. Van Dam-Stokkink, C.: Nederl. Tijdschr. v. Geneesk. **2**:1348, 1924.
17. Davis, G. A.: Arch. Pediat. **41**:200, 1924.
18. Reuben, M. S., and Smith, A. DeG.: Arch. Pediat. **41**:529, 1924.
19. Lemaire, H.: Nourrisson **13**:44 (Jan.) 1925.
20. Lozano, A. R.: Arch. españ. d. pediat. **10**:321, 1926.
21. Nassau, E., and Zweig, H.: Ztschr. f. Kinderh. **39**:484, 1925.
22. Wahlquist, H. J., and Myers, J. A.: Am. Rev. Tuberc. **14**:461, 1926.
23. Langer, H.: Beitr. z. klin. d. Tuberk. **64**:515, 1927.
24. Asserson, M. A.: Am. Rev. Tuberc. **16**:359 (Oct.) 1927.
25. Mandl, F.: Ztschr. f. Kinderh. **45**:487, 1928.

Every one knows that tuberculous meningitis or generalized miliary tuberculosis is fatal in practically every case. It is the study of these advanced cases of tuberculosis or the statistics based on observations made at autopsy that lead to the generally held opinion that a tuberculous infection during the first year of life is a dangerous sign and leads to an active, generalized tuberculosis.

It seems to me that in order to gain a fair idea of the fate of tuberculous infants, the following conditions must be met: 1. Dispensary as well as hospital patients must be studied. 2. The number of patients studied must be large, otherwise definite conclusions cannot be drawn. 3. The patients must be followed up for a number of years; the longer the follow-up period, the better.

THE PLAN OF INVESTIGATION

I therefore undertook to investigate this problem along the following lines: I first examined all the dispensary and hospital records for the past eight years at Professor Pirquet's Children's Hospital; the dispensary records previous to 1920 were no longer kept and therefore could not be studied. After over 70,000 records had been examined, I found 901 records of children who had been infected during the first three years of life. Each of the 901 patients showed at least a definitely positive tuberculin reaction. This tuberculin reaction was always recorded in millimeters, thus eliminating the subjective feelings of the examiner in interpreting the tests. Many of the patients also showed positive roentgenologic and fluoroscopic observations, recorded by such authorities as Wimberger, Rach and Priesel. Many of the patients studied had definite pulmonary conditions, and in some cases poor prognoses were offered to the parents. I have had a number of cases of spina ventosa, scrofuloderma, tuberculous pleurisy and even papulonecrotic tuberculids. The only cases not studied were cases of tuberculous meningitis, generalized miliary tuberculosis and tuberculous pneumonia. Letters were sent to all the 901 patients, inviting them to return to the clinic for reexamination. I soon found that the msot optimistic expectations were surpassed, and that many more infants returned for reexamination than I had hoped. I then discontinued the examination of patients who had first been infected during the second half of the third year of life. This left me with 825 patients, of whom 421 could not be followed up.

Each patient received a complete physical examination, followed by a tuberculin test and a fluoroscopic examination; in some cases roentgenograms were taken. The fluoroscopic examination was done under the direction of Dr. R. Priesel, head of the roentgenology department, and only his observations were recorded.

COMMENT ON TABLES PRESENTED

The complete records contain the histories of contagion, probable source of infection, the results of the last tuberculin tests and the various diseases which the infants have had between the time of the first infection and the last examination. As these facts are not so important, I did not include them in this paper.

TABLE 1.—*Present Status of Patients Tuberculously Infected During First Half Year of Life*

Types of Cases	Present Status	Year of First Examination							Total All Years
		1926	1925	1924	1923	1922	1921	1920	
Pirquet positive	Living	1	1	2	3	3	0	3	13
	Dead	0	0	2	1	0	0	0	3
Hilum tuberculosis	Living	0	2	1	0	0	3	1	7
	Dead	0	0	0	0	0	1	0	1
Spina ventosa	Living	..	..	..	..	..	..	1	1
	Dead	..	..	..	..	..	..	0	0
Epituberculosis	Living	..	..	3	..	..	..	..	3
	Dead	..	..	0	..	..	..	..	0
Papulonecrotic tuberculid	Living	..	..	0	..	..	..	..	0
	Dead	..	..	1	..	..	..	..	1
Total	Living	1	3	6	3	3	3	5	24
	Dead	0	0	3	1	0	1	0	5

A mortality of 17.2 per cent

TABLE 2.—*Present Status of Patients Tuberculously Infected During Second Half of First Year of Life*

Types of Cases	Present Status	Year of First Examination							Total All Years
		1926	1925	1924	1923	1922	1921	1920	
Pirquet positive	Living	3	4	6	10	9	7	4	43
	Dead	0	0	0	0	1	0	0	1
Hilum tuberculosis	Living	3	2	5	2	4	1	2	19
	Dead	0	0	0	0	1	0	1	2
Scrofuloderma	Living	0	2	1	0	0	1	0	4
	Dead	0	0	0	0	0	0	0	0
Papulonecrotic tuberculid	Living	1	0	1	..	..	..	..	2
	Dead	0	0	0	..	..	..	..	0
Spina ventosa	Living	..	..	2	0	1	..	0	3
	Dead	..	..	0	1	0	..	0	1
Pleuritis tuberculosa	Living	..	..	..	1	..	..	..	1
	Dead	..	..	..	1	..	..	..	1
Epituberculosis	Living	..	..	1	..	..	..	..	1
	Dead	..	..	0	..	..	..	..	0
Total	Living	7	8	16	13	14	9	6	73
	Dead	0	0	0	2	2	0	1	5

A mortality of 6.84 per cent

Tables 1, 2, 3, 4 and 5 show the mortality of the patients, grouped according to the time of infection and the years when they had first been examined. Of course, it is probable that many of the patients who are placed in the group of those infected at a certain age had been infected much earlier. Since, however, there is no way of finding out the exact time when infection occurred, I have grouped all these

patients according to the time when the tuberculous infection was first definitely diagnosed. Table 6 gives the total number of patients examined, the type of tuberculous infection, the year when the patient was first examined and the mortality rate.

Table 7 shows the present fluoroscopic and roentgenologic observations. Fluoroscopic examination often showed the Ghon tubercle when

TABLE 3.—*Present Status of Patients Tuberculin Positive During First Half of Second Year of Life*

Types of Cases	Present Status	Year of First Examination							Total All Years
		1926	1925	1924	1923	1922	1921	1920	
Pirquet positive	Living	1	4	12	10	8	3	3	41
	Dead	0	0	0	0	1	0	0	1
Hilum tuberculosis	Living	1	3	11	4	2	3	2	26
	Dead	0	0	1	0	0	1	1	3
Scrofuloderma	Living	..	1	2	1	..	..	..	4
	Dead	..	0	0	0	..	..	..	0
Spina ventosa	Living	..	..	..	1	1	..	1	3
	Dead	..	..	..	0	0	..	0	0
Pleuritis tuberculosa	Living	..	..	0	..	..	..	..	0
	Dead	..	..	1	..	..	..	..	1
Epituberculosis	Living	..	1	1	..	1	..	..	3
	Dead	..	0	0	..	0	..	..	0
Total	Living	2	9	26	16	12	6	6	77
	Dead	0	0	2	0	1	1	1	5

A mortality of 6.1 per cent

TABLE 4.—*Present Status of Patients Tuberculin Positive During Second Half of Second Year of Life*

Types of Cases	Present Status	Year of First Examination							Total All Years
		1926	1925	1924	1923	1922	1921	1920	
Pirquet positive	Living	8	10	17	22	10	3	2	72
	Dead	0	0	0	0	0	0	0	0
Hilum tuberculosis	Living	6	11	11	10	3	3	1	45
	Dead	0	0	0	0	0	0	0	0
Scrofuloderma	Living	1	..	1	1	2	..	..	5
	Dead	0	..	0	0	0	..	..	0
Spina ventosa	Living	..	1	..	2	..	..	..	3
	Dead	..	0	..	0	..	..	..	0
Pleuritis tuberculosa	Living	..	..	2	..	..	..	..	2
	Dead	..	..	0	..	..	..	..	0
Erythema nodosum	Living	..	..	..	1	..	..	1	2
	Dead	..	..	..	0	..	..	0	0
Papulonecrotic tuberculid	Living	..	..	..	..	..	3	..	3
	Dead	..	..	..	..	..	0	..	0
Total	Living	15	22	31	36	15	9	4	132
	Dead	0	0	0	0	0	0	0	0

No mortality

the roentgenogram failed to show it. Frequently, the Ghon tubercle was seen only during deep inspiration; often it lay at the base of the lung, and at other times the ribs and clavicles covered it. A negative roentgenogram does not exclude the presence of the Ghon tubercle. Table 7 brings out the fact that considerable time must elapse between

the entrance of the tubercle bacillus into the lung and the time of the recognition of the Ghon tubercle fluoroscopically and roentgenologically. The percentage of patients in whom the Ghon tubercle was seen fluoroscopically or roentgenologically varied from 8 per cent of patients who had been followed up for from one to two years after the primary

TABLE 5.—*Present Status of Patients Tuberculin Positive During First Half of Third Year of Life*

Types of Cases	Present Status	Year of First Examination							Total All Years
		1926	1925	1924	1923	1922	1921	1920	
Pirquet positive	Living	0	7	9	20	12	4	0	52
	Dead	0	0	0	0	0	0	0	0
Hilum tuberculosis	Living	0	6	5	9	2	0	1	23
	Dead	0	0	0	0	0	0	0	0
Scrofuloderma	Living	..	..	1	..	1	..	..	2
	Dead	..	..	..	..	..	0	..	0
Spina ventosa	Living	..	..	..	..	..	1	..	1
	Dead	..	..	..	..	..	0	..	0
Pleuritis tuberculosa	Living	..	1	1	..	1	..	..	3
	Dead	..	0	0	..	0	..	..	0
Epituberculosis	Living	..	1	..	..	..	..	..	1
	Dead	..	0	..	..	..	..	..	0
Total	Living	0	13	13	29	16	5	0	76
	Dead	0	0	0	0	0	0	0	0

No mortality

TABLE 6.—*Total Number of Patients Examined and Their Present Status*

Types of Cases	Present Status	Year of First Examination							Total All Years
		1926	1925	1924	1923	1922	1921	1920	
Pirquet positive	Living	13	26	46	65	42	17	12	221
	Dead	0	0	2	1	2	0	0	5
Hilum tuberculosis	Living	10	24	33	25	11	10	8	121
	Dead	0	0	1	0	1	2	2	6
Scrofuloderma	Living	1	3	5	2	3	1	..	15
	Dead	0	0	0	0	0	0	..	0
Papulonecrotic tuberculid	Living	1	..	1	..	..	3	..	5
	Dead	0	..	1	..	..	0	..	1
Spina ventose	Living	0	1	2	3	2	1	2	11
	Dead	0	0	0	1	0	0	0	1
Pleuritis tuberculosa	Living	0	1	3	1	1	0	..	6
	Dead	0	0	1	1	0	0	..	2
Epituberculosis	Living	..	2	5	0	1	0	..	8
	Dead	..	0	0	0	0	0	..	0
Erythema nodosum	Living	..	..	..	1	..	..	1	2
	Dead	..	..	..	0	..	..	0	0
Total	Living	25	57	95	97	60	32	23	389
	Dead	0	0	4	3	4	2	2	15

A total mortality of 3.71 per cent

infection to 34.7 per cent of patients who had been followed up for from seven to eight years.

The location of the Ghon tubercle, according to the lobes of the lungs, is given in table 8. The fluoroscopic examination was always performed under the direction of Dr. R. Priesel, head of the roentgenologic department, and only his observations, as well as the previous

observations of Dr. Wimberger and Dr. Roch, are given in these tables. Dr. Priesel will consider the complete fluoroscopic and roentgenologic observations in a separate paper.

CONCLUSIONS

1. Four hundred and four tuberculous infants, varying in age from 4 months to 2½ years, were followed up for a period of from one to eight years.

2. When first examined, 221 of the 404 showed only a positive tuberculin reaction, 121 showed hilum tuberculosis, fifteen showed

TABLE 7.—*The Present Fluoroscopic and Roentgenologic Observations*

Number of Patients			Ghon Tubercle		Calcified Hilum Glands		Ghon Tubercle and Calcified Glands	Increased Hilum Shadows	Pleuritis	Negative	
First Examined in	Number	Duration of Infection, Years	No.	%	No.	%				No.	%
1920	23*	From 7 to 8	8	34.7	14	60.8	7	4	2	2	8.7
1921	32	From 6 to 7	11	34.3	18	56.2	11	10	2	0	...
1922	60	From 5 to 6	12	20	28	46.6	11	19	6	3	5
1923	97	From 4 to 5	34	35	35	36	24	19	10	14	14.4
1924	95	From 3 to 4	25	26.3	34	35.5	17	31	15	16	16.8
1925	57	From 2 to 3	14	24.5	18	31.5	14	20	6	9	15.7
1926	25	From 1 to 2	2	8	2	8	1	10	5	6	24
Total....	389		106		149		95	113	46	50	

* One case with a cavity in the upper lobe of left lung.

TABLE 8.—*The Location of the Ghon Tubercle, According to the Various Lobes of the Lung*

	Number	Per Cent
Lower lobe of right lung	35	33.009
Lower lobe of left lung	22	20.75
Upper lobe of right lung	21	19.85
Upper lobe of left lung	15	14.15
Middle lobe of right lung	13	12.26
Total	106 Ghon tubercles	

scrofuloderma, five showed papulonecrotic tuberculids, eleven showed a spina ventosa, six showed a tuberculous pleuritis, eight showed an epituberculosis and two showed an erythema nodosum.

3. There were fifteen deaths in 404 cases, or a mortality rate of 3.71 per cent.

4. Twenty-nine of the 404 infants were infected during the first six months of life. There were five deaths in the twenty-nine cases, or a mortality rate of 17.2 per cent.

5. Seventy-three of the 404 infants became infected with tuberculosis during the second half of the first year of life. There were five deaths, or a mortality rate of 6.84 per cent.

6. Seventy-seven of the 404 infants became infected with tuberculosis during the first half of the second year of life. There were five deaths, or a mortality rate of 6.49 per cent.

7. None of the infants who had been infected after the first half of the second year of life died.

8. The fluoroscopic and roentgenologic observations showed either a Ghon tubercle or calcified hilum glands in a certain percentage of all patients who were followed up for a varying period of years: from seven to eight years, 95.5 per cent; from five to seven years, 90.5 per cent; from five to six years, 66.6 per cent; from four to five years, 71 per cent; from three to four years, 61.8 per cent; from two to three years, 56 per cent, and in only 16 per cent of the patients who had been followed up for one or two years.

9. The location of the Ghon tubercle according to the lobes was as follows: lower lobe of the right lung, 33.009 per cent; lower lobe of the left lung, 20.75 per cent; upper lobe of the right lung, 19.85 per cent; upper lobe of the left lung, 14.15 per cent, and middle lobe of the left lung, 12.26 per cent.

10. The resistance of the infant to a tuberculous infection, even during the first six months of life, is high. An infant with a positive tuberculin reaction or even with a definitely recognizable lesion (with the exception of tuberculous meningitis, miliary tuberculous and ulcerocaseous pulmonary tuberculosis) should not be given a poor prognosis.

THE PERCUTANEOUS TUBERCULIN REACTION *

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CHICAGO

In a recent article, Stewart [1] described a modification of the Pirquet test by which a single prick with an ordinary needle through a drop of tuberculin is substituted for the usual scarification with a blunt instrument. The chief advantages of this procedure are that it causes less pain and is more rapid than the scarification method. It seems worth while to call attention to a simple and painless method which is apparently little used in the United States.

The inunction test, described by Moro and Doganoff [2] in 1907 and later elaborated by Moro [3] alone, was made by rubbing a little tuberculin ointment into the unabraded skin. The material used was old tuberculin mixed with equal parts of hydrous wool fat. The percentage of positive reactions obtained by this means was, however, too small to make the test of value in the diagnosis of tuberculosis, and it was abandoned by Moro himself. In 1913, Wegerer [4] modified and somewhat improved the method by using undiluted old tuberculin. Then, in 1919, Hamburger and Stradner [5] concentrated old tuberculin over the steam bath to constant weight, and in this way obtained a more active substance.[6] A further improvement was introduced by Widowitz,[7] who found the number of positive reactions increased by rubbing the skin with ether to remove all fat from the pores before making the injection, thus facilitating absorption of the ointment. The present method of performing the modified Moro test at the Children's Clinic in Graz is as follows: The skin over the sternum is rubbed with ether until hyperemia occurs. A piece of the concentrated old tuberculin, the size of a pinhead, is vigorously rubbed in with the finger-tips. The result is read at the end of forty-eight hours. Usually the reaction appears

* Submitted for publication, Dec. 6, 1928.

* From the Children's Clinic, Graz, Austria.

1. Stewart, C. A.: The Pirquet Test, Am. J. Dis. Child. **35**:388 (March) 1928.

2. Moro, E., and Doganoff, A.: Zur Pathogenese gewisser Integumentveränderungen bei Skrofulose, Wien. klin. Wchnschr. **20**: 933, 1907.

3. Moro, E.: Ueber eine diagnostische verwertbare Reaktion der Haut auf Einreibung mit Tuberkulinsalbe, München. med. Wchnschr. **55**: 216, 1908.

4. Wegerer: Studien über Tuberculin-Percutanreaktionen, Med. Klin. **9**: 575, 1913.

5. Hamburger, F., and Stradner, F.: Eine Verbesserung der perkutanen Tuberkulinreaktion (Moro), München. med. Wchnschr. **66**: 439, 1919.

6. This material is now manufactured and dispensed in collapsible tubes by Dr. Fresenius, Hirsch-Apotheke, Frankfort am Main.

7. Widowitz, P.: Ueber eine modifizierte perkutane Tuberkulinprobe, München. med. Wchnschr. **69**: 233, 1922.

within twenty-four hours, but occasionally it is delayed for three or four days, thus corresponding to the torpid reaction described by Pirquet.

Three grades of positive reactions may be described. The weakest consists of several small scattered papules at the site of inunction, with scarcely any reddening. A moderate reaction is shown by a larger group of papules, with definite reddening. In the strong reaction a marked folliculitis appears, with minute vesicles or even pustules and intense inflammation. There may be some itching. The milder reac-

Fig 1.—Mild percutaneous tuberculin reaction at forty-eight hours.

tions persist for several days; the stronger may be visible for a few weeks. Possible but rare sources of error are diffuse reddening or punctate reddening of the pores without folliculitis, as may occur in a sensitive skin. For a positive test there must be definite papules.

If properly performed with concentrated tuberculin, the Moro test yields fully as many positive results as the Pirquet test. Stradner [8] reported reactions in 84 per cent of infected persons with the modified percutaneous test, 51.1 per cent with the original Moro test and 76.6 per

8. Stradner, F.: Ueber die perkutane Reaktion mit äusserst eingeengten Tuberkulin, Beitr. z. Klin. d. Tuberk. **45:** 31, 1920.

cent with the cutaneous method. Wallgren [9] found 83 per cent of infected persons reacting positively to the percutaneous, and 76 per cent to the cutaneous test. Czickeli's [10] figures include 47 per cent of positive reactions to the original percutaneous test, 80.3 per cent to the modified percutaneous test and 66.6 per cent to the cutaneous test. The children who gave negative reactions but who later proved to be suffering from latent or active tuberculosis included many with meningitis, miliary tuberculosis and advanced pulmonary disease and a few with other acute infections. When these cases in which the skin tests are commonly negative are omitted, the percentage of positive reactions is raised to 91.6. Another class of persons who may fail to react to the

Fig. 2.—Marked percutaneous tuberculin reaction at forty-eight hours.

test are those with latent tuberculosis who have been infected some years previously and who have had no opportunity for reinfection. Since a period of hypersensitiveness sets in from six to seven days after the use of tuberculin, a repetition at this time may give a positive result in a child who previously gave a negative reaction but who is infected at the time of the present test.

The percutaneous test has the merit of absolute painlessness, an advantage when dealing with small children. On account of the sim-

9. Wallgren, A.: Hamburgers perkutane Tuberkulinreaktion, München. med. Wchnschr. **71:** 1017, 1924.

10. Czickeli, H.: Ueber die Brauchbarkeit verschiedene Tuberkulinisierungsmethoden zu diagnotischen Zwecken, Monatschr. f. Kinderh. **29:** 242, 1925. Czickeli, H., and Haller, R.: ibid., Wien. klin. Wchnschr. **38:**138, 1925.

plicity of the test, as it requires only the tube of tuberculin and some ether, and no instrument that must be sterilized, it is particularly convenient for house calls and for testing large numbers of children. In schools and other institutions there cannot be any objection on the part of parents or children to this simple and painless procedure, which does not involve pricking or wounding of the skin. The absence of instruments spares the child the fear so often excited by the display of any instrument however simple.

As has been mentioned, from 15 to 20 per cent of the percutaneous tests are unreliable as indicating tuberculous infection; this is true chiefly in advanced cases of tuberculosis or during acute fever. Therefore, while a negative reaction to the percutaneous test is sufficient to exclude tuberculosis in the routine examination of apparently healthy children, it must at times be followed by one of the more sensitive tests. This is necessary in scientific investigations and in examining the underweight child with symptoms suggestive of tuberculosis in whom it is important to try to rule out this condition. Both Reuschel [11] and Hamburger [12] pointed this out in 1908. They described the local subcutaneous reaction, which is not to be confused with the general febrile reaction following injection or larger amounts of tuberculin. At the Children's Clinic, it is the custom to inject 0.01 mg. of old tuberculin subcutaneously on the day following a negative percutaneous test, and if necessary, to follow this at from twenty-four to forty-eight hour intervals by injections of 0.1 and 1 mg. It is important to observe the time intervals exactly, so as to make each injection during a negative phase and not during the period of hypersensitivity that occurs about five or six days after an injection. In this way there is a smaller possibility of severe febrile reactions. The reactions are noted after forty-eight hours. A positive reaction consists in infiltration and reddening of the area of injection for at least three days. Usually the infiltration is present on the day following the injection, but delayed reactions should be watched for. A transient erythema may be present on the day following the injection of 1 mg. of tuberculin; if the child continues to give a negative reaction to this dose, the possibility of infection can practically be excluded.

The subcutaneous is preferred to the intracutaneous method on account of its greater simplicity. It is more easily and rapidly per-

11. Reuschel, F.: Vergleichende Bewertung der Tuberkulinreaktionen im Kindesalter, München. med. Wchnschr. **55**: 397, 1908.

12. Hamburger, F.: Ueber den Wert der Stichreaktion nach Tuberkulininjektion, Wien. klin. Wchnschr. **21**: 381, 1908; Die Ueberlegenheit der Stichreaktion über die Kutanreaktion, München. med. Wchnschr. **66**: 100, 1919; Ueber die perkutane Anwendung des Tuberkulins, ibid. **69**: 1664, 1922; Ueber die intrakutane und subkutane Lokalreaktion, Wien. klin. Wchnschr. **39**: 1247, 1926.

formed and causes less discomfort to the patient; it is therefore convenient for house and office practice, especially in dealing with unruly children. If the smaller dose is given first and if the suggested time intervals are observed, there is little danger of a febrile reaction. The results are read with equal ease and are just as reliable by the two methods.

SUMMARY

A simple and reliable method for testing children for tuberculous infection is described. The modified percutaneous test, followed in certain cases by the local subcutaneous test, is preferred to other procedures on account of reliability combined with greater ease of performance and less discomfort to the patient.

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THYROTOXICOSIS IN CHILDHOOD

EARLY DIAGNOSIS AND RADIUM THERAPY *

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In 1851, more than half a century after Parry [1] had recorded the first authentic case of exophthalmic goiter in the adult, Romberg and Henoch [2] were the first to report a case in a child, aged 14. Almost half a century later, in 1896 and 1897, Steiner,[3] in a comprehensive study of exophthalmic goiter in childhood, was able to collect from the literature only thirty-one cases in children less than 15 years of age. On consulting Sattler,[4] when one learns that 1,391 contributions on exophthalmic goiter had appeared before the date of Steiner's publication, one obtains a vivid and graphic impression of the excessive rarity of exophthalmic goiter in childhood as reflected in the medical literature at the close of the nineteenth century.

Nevertheless, this impression of the excessive rarity of thyrotoxicosis in childhood, which is being continually emphasized in the medical literature, is no longer entirely in agreement with the facts. In 1910, only thirteen years after the appearance of Steiner's publication, Sattler [4] was able to find 184 cases of exophthalmic goiter in children among 3,477 cases in persons of all ages compiled from the literature. Within the past decade and a half, the number of cases recorded has been considerably on the increase. One hundred and twenty-one cases have been reported by the following three observers alone: Bram,[5] forty-three cases; Dinsmore,[6] forty-eight cases, and Helmholz,[7] thirty

* Submitted for publication, Nov. 17, 1928.

* From the Radium Clinic, Beth Israel Hospital.

1. Parry, C. H.: Collections from the Unpublished Writings, 1825, vol. 2, p. 111.

2. Romberg, M. H., and Henoch, E.: Klinische Wahrnehmungen und Beobachtungen, abstr. in Steiner, F.: Morbus Basedow im Kindesalter, Arch. f. Kinderh. **20**:321, 1896.

3. Steiner, E.: Morbus Basedow in Kindesalter, Arch. f. Kinderh. **20**:321, 1896; ibid. **21**:128, 1897.

4. Sattler, H.: Die Basedow'sche Krankheit, Leipsic, 1910, vol. 2.

5. Bram, I.: Goiter: Nonsurgical Types and Treatment, New York, The Macmillan Company, 1924.

6 Dinsmore, R. S.: Hyperthyroidism in Children, Surg. Gynec. Obst. **42**:172 (Feb.) 1926.

7. Helmholz, H. F.: Exophthalmic Goiter in Childhood, J. A. M. A. **87**:157 (July 17) 1926.

cases. A careful review of the recent literature shows that not only clinics for diseases of the thyroid gland and specialists in conditions of the thyroid but the medical profession at large are meeting such cases more frequently than in former years. Moreover, from a study of the problem of exophthalmic goiter both in life and in the literature I am thoroughly convinced that the disease, especially in its formes frustes,[8] is much more prevalent in childhood than the medical literature would lead one to believe.

Although exophthalmic goiter in childhood is a decidedly less frequent occurrence than in adult life, the numerous available case reports in the literature furnish incontestable evidence that except for minor variations the clinical manifestations in children are essentially the same as those in adults. Only choreiform movements have been noted more frequently in children than in older persons.[4] These choreiform movements differ from classic choreic movements by being purposeful. As Helmholz [7] aptly said, "There is the same urge towards movements as in chorea, but in exophthalmic goiter the movements are purposeful and coordinated."

With this single variation, a careful study of the clinical records reveals no essential difference in symptoms and course from those in adults. Not only mild and moderately severe types have been observed, but also very severe forms with fatal issue. Of Sattler's [4] sixty-two cases in which late results are known, six patients died as the result of the disease, yielding a mortality rate of 9.68 per cent. The youngest patient among these six fatal cases was a boy, aged 2½ years. The case of this patient, observed by Schwekendiek,[9] ran an acute course, with marked bilateral exophthalmos, bilateral corneal ulceration and panophthalmitis, and the patient died with symptoms of severe toxemia and myocardial insufficiency four months after the onset of the first symptoms.

As in adults, not all children who withstand even the severer onslaught of the disease recover completely spontaneously or even after medical therapy. Of Sattler's [4] sixty-two patients followed up, only nineteen, or 30.64 per cent, were pronounced cured and twenty-one markedly improved. Four were only moderately improved and twelve, or 19.35 per cent, were only slightly improved.

Impressed by the gravity of exophthalmic goiter in childhood as well as in adult life and the inadequacy of mere medical measures to cope fully with this problem, surgical intervention gradually began to gain favorable notice. The first operation for exophthalmic goiter, to my

8. Trousseau, A.: Du goitre exophthalmique ou maladie de Grave, Clin. méd. de l'Hôtel-Dieu de Paris **2**:614, 1862. Helmholz (footnote 7).

9. Schwekendiek: Ein Fall von Morbus Basedowii bei einem 2½ jahriger Kinde, Allg. med. Centr.-Ztg. **52**:1081 (Oct. 13) 1883.

knowledge, was performed by Charles H. Mayo [10] in 1906, on a girl, aged 7. Excision of the right lobe was done. In 1914, Lewis [10] reported from the Mayo Clinic five operative cases of exophthalmic goiter in children less than 8 years of age. The youngest child was 4 and the oldest 8. There were no operative deaths, and the children were improved. How long after operation the complete control of the symptoms occurred, Lewis did not state.

Less fortunate than the first experience at the Mayo Clinic were the results in the case of a child, aged 7, reported by Railliet [11] in 1914. In this case, thyroidectomy was followed by death within twenty-four hours. Although favorable operative results have been recorded since that time by several observers,[12] the risk of operation on these patients is by no means negligible. This fact was emphasized in Helmholz's recent report from the Mayo Clinic. Two of twenty-four children on whom operations were performed lost their lives as the result of the operation. And, what is more important, one of these deaths "was in the group of patients who received compound solution of iodin before operation."

That surgical intervention, even the most expert at the Mayo Clinic, fortified by preoperative medication with iodine, carries with it a mortality rate in exophthalmic goiter in children is thus an established fact. But are the claims of Dinsmore [6] true that "such cases are never cured . . . unless the gland is removed" by the surgeon's knife, and therefore surgical intervention with its attendant mortality is a justifiable procedure even before other equally efficient or even more efficient nonsurgical measures have been given a thorough trial? I maintain that Dinsmore's surgical claims can no longer be substantiated. I am thoroughly convinced that operation is not the only successful method of local attack on the thyroid gland in the treatment for exophthalmic goiter. I have had ample opportunity to be convinced that in radium therapy there is a safe, efficient, bloodless agent that can yield as brilliant results as surgical intervention, without its attendant mortality.

What radium has achieved in the treatment for exophthalmic goiter and toxic adenoma in adults was dealt with in two previous communications.[13] What radium promises for the successful treatment for

10. Lewis, W. H.: Juvenile Hyperthyroidism, St. Paul M. J. **16**:91, 1914.

11. Railliet, M. G.: Goitre exophthalmique chez une fillete de sept ans, herédité similaire, Arch. de méd. d. enf. **17**:682, 1914.

12. Sawyer, A. W.: Toxic Goiter in a Girl Ten Years Old, Ann. Surg. **64**:371, 1916. Buford, R. K.: Hyperthyroidism in Children Before Puberty, J. A. M. A. **78**:1533 (May 20) 1922. Heiman, H.: Exophthalmic Goiter in Childhood with Some Unusual Manifestations, Am. J. Dis. Child. **26**:216 (Sept.) 1923. McGraw, A. B.: Juvenile Exophthalmic Goiter, Surg. Gynec. Obst. **47**:25 (July) 1928.

13. Ginsburg, S.: Radium Treatment of Exophthalmic Goiter, to be published; Toxic Adenoma of the Thyroid, to be published in Arch. Int. Med..

exophthalmic goiter and toxic adenoma in children can be gleaned from a careful study of the following case reports from the Radium Clinic of Beth Israel Hospital.

REPORT OF CASES

CASE 1.—*History.*—Tillie S., aged 14, who was referred to the Radium Clinic of Beth Israel Hospital on Feb. 5, 1925, by Dr. J. C. Seal of New York, complained chiefly of nervousness, goiter, exophthalmos and excessive perspiration of seven years' duration. In 1917, at the age of 7, persistent nervousness noted by the parents led to a medical consultation. A diagnosis of "nervous heart" of unknown origin was made. Seven years later, in October, 1924, the school nurse was the first to discover the presence of a goiter. After consultation with the family physician, she was immediately referred to a well known surgeon, who specializes in operations on the thyroid gland, who treated her medically for two months. The result was a progressive aggravation of all the symptoms. The thyroid gland showed further increase in size, and bilateral exophthalmos developed. She grew more nervous and suffered from excessive perspiration. Thyroidectomy was then urged. The parents refused operative intervention and were referred to the Radium Clinic of Beth Israel Hospital for radium therapy.

Examination.—The patient was a well developed and well nourished girl, weighing 111 pounds (50.3 Kg.). The eyes showed bilateral exophthalmos and weakness of the right external rectus. The thyroid gland was diffusely enlarged, with predominance of the right lobe and isthmus. The consistency of the gland was soft elastic. Irregularities and nodules were absent. Bruit and thrill were present. The circumference of the neck through the seventh cervical vertebra and the midthyroid region measured 39 cm. On percussion the heart was found to be moderately enlarged. The sounds were regular and forceful; no murmurs were present. The aortic second sound was accentuated. The rate was 132 per minute. The blood pressure was 120 systolic and 60 diastolic. The chest, lungs and abdomen were normal. The fingers showed a fine tremor. The knee reflexes were exaggerated.

Laboratory Data.—Roentgen examination of the chest showed enlargement of the cardiac shadow. Examination of the blood showed: red blood cells, 5,040,000; hemoglobin, 85 per cent; white blood cells, 7,600; polymorphonuclears, 49 per cent; eosinophils, 1 per cent; basophils, 1 per cent; large lymphocytes, 3 per cent; mononuclears, 1 per cent, and small lymphocytes, 45 per cent. The urinalysis showed a trace of albumin and a few white blood cells. The basal metabolism was plus 18 per cent.

The diagnosis was exophthalmic goiter.

Course Under Radium Therapy.—Between Feb. 10 and March 25, 1925, the patient received 3,600 mg. hours of radium to the thyroid region, with the "block" (fig. 1) at a distance of 3 cm., and 1,800 mg. hours to the thymus region. The result was gratifying. Within one month after the course of treatments with radium was completed there was a great improvement in the constitutional symptoms and a shrinkage of the neck from 39 to 36 cm. The blood pressure became normal and the basal metabolic rate decreased to +7 per cent. In May, the second course of radium therapy was started. After receiving a suberythema dose to the thymus region, she lost all subjective complaints and therefore refused to go on with any further treatments.

She was reexamined in January, 1926. Subjectively, she felt entirely well and had no complaints. The neck had shrunken from the original 39 cm. to 35 cm.

However, she still appeared somewhat nervous and presented slight tachycardia and exophthalmos. Further radium therapy was suggested, but was declined because the patient considered herself perfectly well. When last heard from in the spring of 1928, she was in a perfect condition of health.

Comment.—The features of special interest in this case are:

1. The onset at the early age of 7 with nervousness as the only symptom, which led to a diagnosis of "nervous heart" of unknown origin.

2. The clinical detection of goiter seven years after the onset of nervousness.

3. The rapid development of all the classic signs of exophthalmic goiter within a few months after the discovery of the enlargement of the thyroid gland.

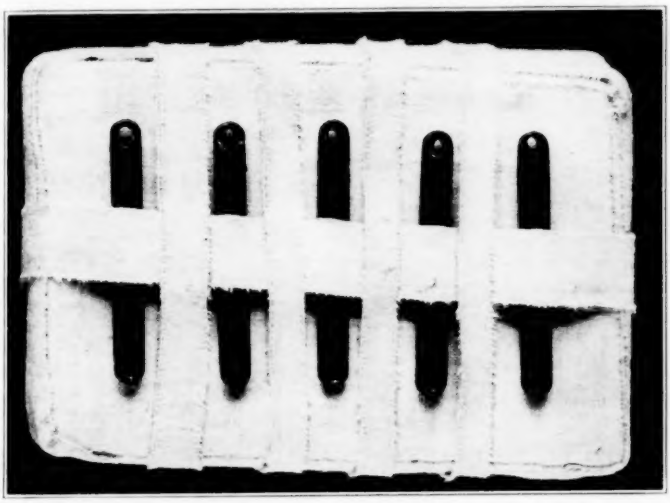

Fig. 1.—Radium "block." The radium "block" is made of balsa wood and is 7 by 5 by 3 cm. It is covered by adhesive plaster. Several layers of gauze are interposed between it and the skin to serve as a cushion and to absorb perspiration. The distribution of the radium capsules is shown above. Each brass capsule, of 1 mm. wall thickness, contains from 10 to 25 mg. of radium in standard steel needles, according to indications. The "block" is strapped in place by means of adhesive plaster and reinforced with a bandage. Three thousand milligram hours constitute an erythema dose.

4. The failure of medical measures to influence favorably the course of the disease.

5. The refusal of thyroidectomy urged by one of the most prominent surgeons who specializes in operations on the thyroid.

6. The splendid physical development and the preservation of 10 pounds (4.5 Kg.) above normal weight with symptoms of exophthalmic goiter developing over a period of years.

7. The favorable response to radium therapy which made operation superfluous.

CASE 2.—*History.*—Rose W., aged 14, admitted to the Radium Clinic on Jan. 14, 1926, was included in the study of "Toxic Adenoma of the Thyroid." However, as it forms the second case of my children's series it will be here reproduced. In October, 1925, the presence of a goiter was detected by the school nurse. For the next three months after its discovery the goiter kept fluctuating in size but was apparently not associated with any toxic symptoms. In December, the child developed nervousness, irritability, loss in weight and disturbed sleep. One month later, she was referred by the family physician to the Radium Clinic, with a diagnosis of toxic goiter.

Examination.—The patient was a well nourished and developed girl of 14, weighing 96 pounds (43.5 Kg.). The face was flushed. The eyes were somewhat prominent, but definite exophthalmos and the other ocular signs of exophthalmic goiter were wanting. The teeth were in good condition. The pharynx was congested. The tonsils were considerably enlarged and congested. The submaxillary and posterior cervical lymph nodes were enlarged. The thyroid gland showed a diffuse enlargement with predominant involvement of the isthmus and right lobe. The right lobe felt firmer than the rest of the gland and was distinctly nodular. Thrill was absent. Bruit was present only over left lobe. The circumference of the neck through the seventh cervical vertebra and the midthyroid region measured 33.5 cm. On percussion the heart was found to be moderately enlarged. Murmurs and irregularities were absent. The rate in the recumbent posture was 140 per minute. The blood pressure was 120 systolic and 70 diastolic. A retromanubrial dulness was present. The lungs and abdomen were normal.

Laboratory Data.—Roentgen examination of the chest showed cardiac enlargement. Electrocardiographic tracings showed simple tachycardia, left ventricular predominance and the T wave inverted in lead 3. Examination of the blood revealed: red blood cells, 4,500,000; hemoglobin, 80 per cent; white blood cells, 6,000; polymorphonuclears, 52 per cent; large lymphocytes, 2 per cent, and small lymphocytes, 46 per cent. The basal metabolism was + 14 per cent. The results of a urinalysis were essentially negative.

The diagnosis was: thyrotoxicosis; toxic adenomatous goiter.

Course Under Radium Therapy.—Treatment with radium was started on Feb. 25 and completed on April 30, 1926. The region of the thymus and the left lobe of the thyroid received 2,300 mg. hours of radium with the "block" at a distance of 3 cm., while the right lobe was given 3,000 mg. hours. There was prompt improvement in subjective symptoms, and within five weeks after the first fractionated dose of radium, the weight increased from 92 to 104½ pounds (41.7 Kg. to 47.4 Kg.). On May 4, the circumference of the neck measured 33 cm. The heart showed only slight acceleration. Reexamination in February, 1927, showed the patient completely free from any subjective complaints. She had gained 20 pounds (9 Kg.) since the first admission to the radium clinic. The pulse was normal. The hand grip was very firm and strong. The neck had shrunken from the original 33.5 cm. to 32.5 cm. The last examination in July, 1928, showed the condition to be practically unchanged.

Comment.—The chief points of interest in this case are:

1. The discovery of a fairly large goiter on routine examination by the school nurse, which may or may not have been a factor in the high-strung condition of the patient from early childhood.

2. The development of moderately toxic constitutional symptoms a few months after the discovery of the goiter.

3. The presence of a large nodular goiter with moderately toxic symptoms and marked tachycardia, with a basal metabolic rate of only plus 14 per cent.

4. The prompt favorable response to treatment with radium and the complete disappearance of subjective complaints with only slight shrinkage in the size of the thyroid gland.

Case 3.—*History.*—Tessie G., aged 13½, was admitted to the radium clinic on Aug. 31, 1926, with the complaint of nervousness, irritability, lacrimose condition, headache, disturbed sleep, loss in weight and enlargement of the neck, of eight and a half years' duration. The exact date of onset was difficult to elicit. It possibly began at the age of 5, when a tendency to a "nervous disposition" and undue emotionalism were noted. These grew progressively more marked as the years passed. At the age of 10½ she began to suffer from frontal headaches and loss in weight in spite of a good appetite. At 11½ an enlargement of the thyroid was first noted, associated with sleeplessness, increased irritability, nervousness and undue emotionalism.

Examination.—The patient was an overdeveloped, bright and alert girl, weighing 140 pounds (63.5 Kg.). The face was flushed, but exophthalmos and other ocular signs of exophthalmic goiter were absent. The thyroid gland showed a diffuse enlargement with predominant involvement of the right lobe. The gland was soft elastic in consistency and freely movable. Bruit and thrill were absent. The circumference of the neck through the seventh cervical vertebra and the midthyroid region measured 33 cm. The heart showed no enlargement. Murmurs and irregularities were absent. The rate was 120 per minute. The lungs, abdomen and extremities were normal. No tremor of the fingers was present.

Laboratory Data.—Roentgen examination of the chest showed the cardiac and pulmonary fields to be normal. Electrocardiographic tracings showed simple tachycardia. Examination of the blood revealed: red blood cells, 4,880,000; hemoglobin, 80 per cent; white blood cells, 8,400; polymorphonuclears, 81 per cent; eosinophils, 4 per cent; mononuclears, 1 per cent, and small lymphocytes, 14 per cent. The urine showed a trace of albumin and a few white blood cells. The basal metabolism was —4 per cent.

Diagnosis.—The diagnosis of this case appeared puzzling. According to the clinical evidence, before the basal metabolic rate was reported, I was inclined to make a diagnosis of forme fruste of exophthalmic goiter. When I looked at the splendid physical and mental development of this young girl with a metabolic rate of —4, I thought that a tentative diagnosis of simple goiter was more justifiable.

Course Under Treatment with Iodine.—As a diagnosis of simple goiter had been made, the patient was placed on a course of compound solution of iodine, 1 minim (0.6 cc.), three times a day. The result was entirely disappointing. After a temporary shrinkage of 0.5 cm., the neck began to enlarge, and on Dec. 2, 1926, the circumference of the neck measured 34.5 cm. The pulse rate in the recumbent position was 124 per minute. The basal metabolic rate was + 3 per cent. The medication with iodine was discontinued and watchful waiting decided on. During the next three months there was no remission in symptoms although the neck returned to its former size, 33 cm. On March 5, 1927, without any aggravation in the subjective complaint, the basal metabolic rate rose to + 36 per cent.

What was the explanation of this sudden rise in metabolism? Was this a case of late iodine thyrotoxicosis or of "iodine hyperthyroidism"? Was I confronted here merely with an exacerbation of the disease in a toxic goiter independent of medication with iodine? Were all the symptoms which this child presented since the age of 5 due to a mildly toxic thyroid condition in which the basal metabolism rose above normal levels only at times?

Careful consideration and weighing of the evidence made me strongly incline to the view that the child had been suffering from a mild thyrotoxicosis for a number of years. As the basal metabolism had risen to + 36 per cent, I thought that radium therapy ought to be given a trial.

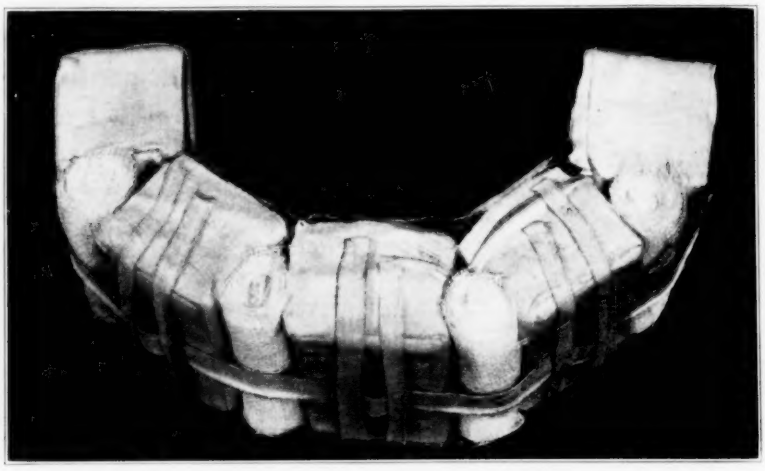

Fig. 2.—Radium "collar." The radium "collar" is made of five blocks of balsa wood, each block measuring 5 by 3 by 3 cm. The blocks are held together by adhesive plaster. Their proper adjustment to the neck is obtained by pledgets of gauze. The distribution of the radium capsules is shown above. Each brass capsule, of 1 mm. wall thickness, contains from 10 to 25 mg. of radium in steel needles, according to indications. The "collar" is strapped in place by adhesive plaster and reinforced by a bandage. Six thousand milligram hours constitute an erythema dose.

Course Under Radium Treatment.—Between March 10 and 24, 1927, the patient was given 6,012 mg. hours of radium to the thyroid gland with the radium "collar" (fig. 2) at a distance of 3 cm. The result was gratifying and highly instructive. On May 5, 1927, she was free from any subjective complaints. The basal metabolism was reduced from + 36 to +4 per cent. The pulse rate, which was from 120 to 150, decreased to from 84 to 100. The circumference of the neck was reduced from 35 cm., immediately before the treatment, to 32.5 cm. Reexamination on April 4, 1928, showed a basal metabolic rate of —6.

She returned in July, 1928, complaining of a mild recurrence of the symptoms. A basal metabolic determination made on July 18 showed a rate of + 22 per cent.

Although the general condition was excellent and the weight had increased 13 pounds (5.9 Kg.) since admission to the clinic, I advised a repetition of the treatment with radium.

Comment.—The salient features of this case deserving special emphasis are:

1. The onset of toxic symptoms at the age of 5 years without any gross clinical evidence of enlargement of the thyroid gland.

2. The onset of loss in weight five and a half years after the development of emotional instability and nervousness.

3. The discovery of enlargement of the thyroid gland six and a half years after the onset of toxic symptoms.

4. The splendid mental and physical development in spite of toxic symptoms of eight and a half years' duration.

5. The low basal metabolic rate, — 4, in spite of definite toxic symptoms extending over a period of years.

6. The erroneous diagnosis of simple goiter which led to iodine therapy followed, either as a coincidence or as a consequence, by an aggravation in all symptoms and a rise in the basal metabolism from — 4 to + 36 per cent.

7. The excellent response to a single course of radium therapy directed only to the thyroid gland.

8. The slight recrudescence in symptoms with a consequent rise in basal metabolism to + 22 one year later, which, I am confident, will be readily controlled by further judicious treatment with radium.

Case 4.—*History.*—Frieda K., aged 15, who was admitted to the radium clinic on June 16, 1927, complained of nervousness, irritability, tachycardia and palpitation, dyspnea on exertion, asthenia, exophthalmos, tremor, enlargement of the thyroid gland, excessive sweating and irregular menstruation. In September, 1926, she began to develop classic symptoms of exophthalmic goiter which became greatly aggravated after medication with iodine. In March, 1927, a thyroidectomy was performed by a prominent surgeon. Three months after the operation, the basal metabolism had dropped from + 55 to + 4 per cent but the clinical symptoms were only slightly relieved.

Examination.—The patient was a well developed and well nourished girl, weighing 137 pounds (62 Kg.). The face was flushed and the eyes showed marked bilateral exophthalmos (fig. 3 *A*). All the ocular signs of exophthalmic goiter were strongly positive. In the lower anterior cervical region there was a transverse supple scar, the result of the operation on the thyroid gland. This gland showed a moderate enlargement of the left lobe and isthmus and a slight enlargement of the right lobe. The gland was soft elastic, and was moderately tender to pressure. A bruit was heard only over the left lobe. On percussion the heart was found to be enlarged. There was a soft systolic apical and pulmonic basal murmur. The heart sounds were regular, 104 and 124 per minute. The chest, lungs and abdomen were normal. There was a tremor of the fingers; a slight edema of the lower extremities was present. The reflexes were normal.

Laboratory Data.—Roentgen examination of the chest was negative. Electrocardiographic tracings showed simple tachycardia and the T wave inverted in lead 3. Examination of the blood revealed: red blood cells, 3,400,000; hemoglobin, 70 per cent; white blood cells, 5,500; polymorphonuclears, 32 per cent, and lymphocytes, 68 per cent. The urine showed a trace of albumin, a few red blood corpuscles and many epithelial cells. The basal metabolism was + 4 per cent.

The diagnosis was: exophthalmic goiter, with little relief from toxic manifestations in spite of thyroidectomy and a normal basal metabolic rate. The patient was to be given radium therapy.

Course Under Treatment with Radium.—Between July 5 and 13, 1927, the patient received 6,000 mg. hours of radium to the thyroid gland with the radium "collar" at a distance of 3 cm. and 3,000 mg. hours to the thymus region with the

Fig. 3.—*A*, exophthalmic goiter in a girl, aged 15, who was unrelieved of symptoms four months after thyroidectomy, before treatment with radium, July, 1927. *B*, after treatment with radium, December, 1928.

"block" at a similar distance. There was prompt and decided improvement in all symptoms, including exophthalmos, and the circumference of the neck shrank from 32 to 30.5 cm. The heart rate, however, persisted at 120 per minute and the blood pressure still registered 115 systolic and 45 diastolic. A restudy of the basal metabolism on Aug. 24, 1927, showed a rate of + 12 per cent. The second course of treatment with radium was therefore given during August and September. This was followed by further improvement in symptoms and a gain of 17 pounds (7.7 Kg.). However, a basal metabolic determination made on Nov. 23, 1927, showed a rate of +22 per cent. Hence, a third course of treatment with radium was carried out in November and December. The result was further improvement in symptoms. In March, 1928, the basal metabolism had dropped to + 8 and the blood pressure registered 140 systolic and 90 diastolic. The pulse still showed a rate of from 84 to 104.

The fourth and last course of radium therapy was given during March and April, 1928. This was followed by a rapid subsidence of all symptoms, including exophthalmos. In August the patient had to undergo a laparotomy for recurring appendicitis. She stood the operation very well and showed no recrudescence of symptoms of exophthalmic goiter. The last examination in December, 1928, showed her fully recovered (fig. 3 *B*) and making fair progress in her school work.

Comment.—The chief points of interest in this case are:

1. The aggravation of all thyrotoxic symptoms after medication with iodine.

2. The failure of thyroidectomy to produce appreciable improvement in symptoms four months after operation in spite of a drop in the basal metabolic rate from + 55 to + 4.

3. The presence of a low basal metabolic rate with marked toxic symptoms and the moderate rise in basal metabolism with improvement in symptoms after radium therapy.

4. The prompt improvement after the first course of treatments with radium and the slower response to further treatments which, nevertheless, were followed by complete recovery when appendicitis arose as a complication.

5. The ease with which the patient went through an abdominal operation to final recovery from the appendicular involvement and the exophthalmic goiter.

CASE 5.—*History.*—Bella W., aged 13, was admitted to the radium clinic on Aug. 16, 1927, her chief complaints being undue nervousness and emotionalism, excessive appetite, exophthalmos, goiter and tremor. In November, 1926, nine months before admission, she developed nervousness, irritability and excessive appetite, and four months later, in March, 1927, the right eye began to bulge. She applied to an eye infirmary and the condition was diagnosed as exophthalmic goiter. During the next few months she was treated medically without any results. The symptoms grew more marked and numerous.

Examination.—The patient was a well developed girl weighing 97½ pounds (44.2 Kg.) (fig. 4 *A*). In her entire bearing, there was marked nervousness, restlessness and emotional instability. The eyes showed bilateral exophthalmos, the right more marked than the left. Stellwag's, Dalrymple's, von Graef's and Möbius' signs were present. The tongue was tremulous. The pharynx was congested. The tonsils were moderately enlarged and congested. The thyroid gland showed a diffuse enlargement, with a few tiny nodules in the isthmus. The consistency of the gland was soft elastic. Mobility was normal. Bruit and thrill were absent. The circumference of the neck through the seventh cervical vertebra and the mid-thyroid region measured 31 cm. The chest and lungs were normal. The heart showed a moderate acceleration and an apical systolic murmur. The abdomen failed to reveal any abnormality. There was a moderate tremor of the fingers.

Laboratory Data.—Roentgen examination of the chest was negative. Electrocardiographic tracings showed simple tachycardia, left ventricular predominence and the T wave inverted in lead 3. Examination of the blood revealed: red blood cells, 4,500,000; hemoglobin, 80 per cent; white blood cells, 6,000; polymorpho-

nuclears, 67 per cent, and lymphocytes, 33 per cent. The Wassermann reaction was negative. The basal metabolism was normal.

The diagnosis was: exophthalmic goiter, with active clinical manifestations in spite of a normal basal metabolic rate reported by the laboratory. Hence, the patient was to be treated actively by radium.

Course Under Treatment with Radium.—Between Sept. 6 and 13, 1927, the patient was given 6,000 mg. hours of radium to the thyroid region with the radium "collar" at a distance of 3 cm. and 1,000 mg. hours to the thymus region with the "block" at a distance of 3 cm. The result was moderate improvement in constitutional symptoms and a gain from 97½ to 104 pounds (44.2 Kg. to 47.2 Kg.). The circumference of the neck was reduced from 31 to 29 cm. The pulse rate varied between 90 and 100. In December, 1927, the second course of treatments with radium was given. Gradual progressive improvement followed. In March, the

Fig. 4.—*A*, exophthalmic goiter in a child, aged 13, before treatment with radium, August, 1927. *B*, after treatment with radium, March, 1928.

patient was free from any subjective complaints. The weight had increased from the original 97½ to 116¾ pounds (52.9 Kg.). The pulse rate was 72 per minute. The hands had lost their tremor. The exophthalmos had definitely receded. The thyroid gland was barely palpable (fig. 4*B*). The last examination on Aug. 7, 1928, showed the improvement persisting. Of special interest was the observation that a stubborn eczema of the ears, which had resisted various local measures for years, had completely disappeared, probably as the result of the radium rays the potency of which extended beyond the immediate area of application.

Comment.—The salient features of this case are:

1. The indefinite onset with a history of nervousness of many years' duration.

2. The onset of an exacerbation with bulimia nine months before admission to the clinic.

3. The development of unilateral exophthalmos leading to primary consultation with an ophthalmologist.

4. The first discovery of the enlargement of the thyroid by the ophthalmologist.

5. The failure of medical therapy to produce improvement in the symptoms.

6. The low basal metabolic rate with classic symptoms of exophthalmic goiter.

7. The clinical disappearance of all toxic symptoms and the subsidence of exophthalmos without any change in basal metabolism except a slight rise at the height of the reaction to radium after the second course of treatment.

CASE 6.—*History.*—Pearl C., aged 12, referred by her family physician in consultation on July 31, 1928, complained chiefly of night terrors, loss in weight, tremor, enlargement of the thyroid gland, irritability, dyspnea, palpitation and tachycardia and diarrhea of one year's duration. The family history was negative. The patient was high-strung but cheerful and sociable, and had many friends. The appetite, bowels and urination had always been normal until the onset of the present illness. Menstruation had not set in. She had measles at the age of 5 years; German measles at 6, and pertussis at 7. She experienced frequent attacks of acute sore throat until three years before examination, when tonsillectomy was performed. There had been no attacks of sore throat since that time.

The illness had started in July, 1927, with frequently recurring night terrors. She would scream out in her sleep and sit up in bed wild-eyed and terrified. The eyes would be widely staring, the heart palpitated and beat rapidly. She could not be aroused. These unaccountable attacks kept recurring until November, 1927, when her mother noticed that the child had been losing weight and had developed a tremor of the fingers, especially marked while doing her writing exercises at school. The next month, irritability at play with other children and enlargement of the thyroid gland were noted. The symptoms grew progressively more marked. In addition, she began to complain of dyspnea, palpitation and tachycardia on exertion and was annoyed by frequent painless, diarrheal stools. In spite of all these complaints no physician was consulted until June, 1928. Examination, including a basal metabolic determination which showed a rate of + 58 per cent, led to a diagnosis of toxic goiter. The child was placed on a compound solution of iodine, 5 minims, three times a day, and was permitted to continue attendance at school. She was reexamined at the end of three weeks and was found greatly improved, with a gain from 78 to 85 pounds (35.4 to 38.6 Kg.). The doses of a compound solution of iodine were continued for several more days and were then stopped. Reexamination by the family physician on July 19, 1928, showed a recurrence of all the former symptoms. The basal metabolic rate was + 34. Iodine therapy was again resumed for a week. Improvement failed to follow, and on July 31 the patient was referred in consultation with special reference as to the advisability of radium therapy.

Examination.—The patient was a well nourished, bright child with a rapidly beating, palpitating heart, the heart beats being visible through the child's clothing at a distance of 8 feet (243.86 cm.). She was markedly nervous and had a spell of faintness during the course of the physical examination. The skull and scalp

were normal. Exophthalmos and the other ocular signs of exophthalmic goiter were absent. The teeth were in good condition. The pharynx was normal. The tonsils were absent. The thyroid gland showed a diffuse enlargement, both granular and nodular. The consistency was harder than normal; the mobility was normal. Bruit and thrill were absent. The carotid vessels showed no undue pulsations. The circumference of the neck through the seventh cervical vertebra and the mid-thyroid region measured 29.5 cm. The transverse diameter was 13 cm.; the right vertical, 6 cm.; the left, 5 cm.; the thickness of the right lobe was 3 cm., that of the left lobe, 1.5 cm. The heart showed a slight increase of the borders. The rate was 110. Murmurs and irregularities were not present. The lungs and abdomen were normal. The knee reflexes were normal.

The diagnosis was: thyrotoxicosis; toxic adenomatous goiter.

Treatment.—Radium therapy was recommended.

Although the medical profession in general believes that toxic adenoma is a distinctly surgical disease, my experience shows that equally good or even better results can be obtained by judicious radium therapy in toxic adenoma, as can be and have been obtained in the treatment for classic exophthalmic goiter.

Comment.—The salient features of this case are:

1. The onset with night terrors.

2. The absence of exophthalmos after one year of moderately severe toxic symptoms with a basal metabolic rate of + 58.

3. The presence of a toxic nodular goiter without exophthalmos in a child, aged 12.

4. The initial improvement in symptoms of a toxic nodular goiter under iodine therapy and the return in symptoms after stoppage of the drug.

COMMENT

Nearly a century and a half has now elapsed since Parry [1] described the first authentic case of exophthalmic goiter. During this period of time the problem of exophthalmic goiter has received the most intensive study and investigation by a host of the most brilliant minds in the medical profession. Nevertheless, the specific etiology of the disease remains just as obscure as when Parry penned his first report. In no other group of patients is this fact of complete ignorance of the specific etiology of exophthalmic goiter more forcibly brought to light than in the study of the development of this disease in childhood. Here, one is frequently at a loss to find either exciting or predisposing causes of the disease. The validity of this disconcerting but incontrovertible fact was especially impressed on me in the clinical investigation of my own series of cases. In spite of the most careful and searching interrogation and investigation, I was completely unable to discover any plausible causes for the origin of the disease in these children.

In the absence of any knowledge of the specific etiology of this disease, is there any specific single diagnostic test to enable one to make a

positive differential diagnosis in every case and in every stage of toxic or exophthalmic goiter, even when the clinical signs are atypical? Some observers believe that the determination of the basal metabolic rate does furnish such a specific diagnostic test. But is this test always a reliable guide or index of the presence or absence of a thyrotoxic condition? Will not other forms of intoxication also raise the metabolic exchange or rate in the body? Has it not been definitely proved that a high basal metabolic rate does occur in a number of diseases other than exophthalmic or toxic goiter?[14] On the other hand, has it not been the experience of every student of thyroid disease to encounter clinically toxic thyroid cases, presenting at times all the classic signs of exophthalmic goiter, which nevertheless showed a normal basal metabolic rate, as has been observed in three of my six cases? The aid derived from basal metabolic determinations in the diagnosis of toxic or exophthalmic goiter is great and exceedingly valuable but is not always an infallible guide or index of the degree of toxicity. It may fail when one most depends on it, for it does not always, as is believed by many members of the medical profession, run parallel with the clinical manifestations of the disease.

Is there any other specific diagnostic laboratory test to aid one in the recognition of the atypical toxic cases? Will a biopsy of the enlarged thyroid gland decide the issue in a questionable case? This procedure has been tried. Recently, Rienhoff[15] of Johns Hopkins, reported a series of exophthalmic goiter cases in which a positive diagnosis was established by this procedure. But is the microscopic picture always a reliable index of the clinical course of the disease? While I thoroughly share the opinion of the numerous pathologists[16] who

14. De Bois, E.: Basal Metabolism in Health and Disease, Philadelphia, Lea & Febiger, 1927.

15. Rienhoff, W. F., Jr.: Involutional or Progressive Changes in the Thyroid Gland in Cases of Exophthalmic Goiter, Arch. Surg. **13**:391 (Sept.) 1926.

16. Greenfield, W. E.: The Bradshaw Lecture on Some Diseases of the Thyroid Gland Delivered Before the Royal College of Physicians, Brit. M. J. **2**:13, 1893. Joffroy, A., and Achard, C.: Contribution a l'anatomie pathologique de la maladie de Basedow, Arch. de méd. expér. et d'anat. path. **5**:807, 1893. Renaut: Corps thyroide et maladie de Basedow, Semaine méd. **15**:327, 1895. Farner, E.: Beitrage zur pathologische Anatomie des morbus Basedowii mit besonderen Berucksichtigung der Strumen, Virchows Arch. f. path. Anat. **143**:509, 1896. Müller, L. W.: Beitrage sur Histologie der normalen und der erkrankten Schilddruse, Beitr. z. path. Anat. u. z. allg. Path. **19**:127, 1896. Hamig, G.: Untersuchungen über morbus Basedowii, Arch. f. klin. Chir. **55**:1, 1897. von Hansemann, D.: Schilddrüse und Thymus bei der Basedow'schen Krankheit, Berl. klin. Wchnschr. **42**:65 (Oct. 30) 1905. Ewing, J.: Exophthalmic Goiter from the Standpoint of Serum Therapy, New York M. J. **84**:1061 and 1114, 1906. Kocher, T.: The Pathology of the Thyroid Gland, Brit. M. J. **1**:1261, 1906. Lewis, D. D.: The Pathological Anatomy of Exophthalmic Goiter, Surg. Gynec. Obst. **3**:476, 1906. MacCallum, W. G.: The Pathology of Exophthalmic Goiter, J. A. M. A. **49**:1158 (Oct. 5)

described a specific or definite pathologic process in the thyroid gland in typical or classic exophthalmic goiter at the most active stage of the disease, it is not the typical or classic case but rather the atypical case that will most frequently present difficulty in diagnosis. In such cases, I am inclined to believe that the observations will more frequently be those that led one of the foremost students [17] of the pathology of goiter to declare, "There is no specific diagnostic pathological microscopic picture in exophthalmic goiter that completely differentiates it from other forms of nontoxic goiter, especially in the active growing phase."

However, even if a biopsy were always conclusive as to diagnosis, will any experienced pediatrician seriously entertain the thought that many mothers would readily submit their children to an operative procedure merely to enable a physician to make a diagnosis in a questionable case.

If the laboratory, including the microscope, cannot always be relied on to aid one in the diagnosis of an atypical or doubtful case, are there no other methods besides a careful clinical study of the signs and symptoms which should always precede and be correlated with any special diagnostic tests?

To this question my answer is: There are two such clinical tests by the two most powerful therapeutic agents in the treatment for all types of goiter. These tests are: the iodine therapeutic diagnostic test and the radium therapeutic diagnostic test.

1. *The Iodine Therapeutic Diagnostic Test.*—In 1820, the same year in which Coindet [18] introduced Courtois' [19] recently discovered element, iodine, in the therapy for goiter, reports began to appear in the medical literature which stressed the occasional marked toxic symptoms that follow the use even of small doses of this new potent agent in the treatment for goiter. More than a century of research has now firmly established the fact recently stressed by Kimball [20] that in questionable

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1907. Kocher, A.: Die histologische und chemische Veränderung der Schilddruse bei morbus Basedowii und ihre Beziehung im Funktion der Druse, Virchows Arch. f. path. Anat. **208**:86, 1912. Wilson, L. B.: The Pathology of the Thyroid Gland in Exophthalmic Goiter, Am. J. M. Sc. **146**:781, 1913. Roussy, G.: Les lésions du corps thyroide dans la maladie de Basedow, Paris, Masson & Cie, 1914. Aschoff, L.: The Goiter Problem: Lectures on Pathology, New York, Paul B. Hoeber, 1924.

17. Marine, D., and Lenhart, C. H.: Pathological Anatomy of Exophthalmic Goiter, Arch. Int. Med. **8**:265 (Sept.) 1911.

18. Rilliet, F.: Mémoire sur l'iodism constitutionnel, etc., presenté a l'academie impériale de médecine, Jan. 2, 1859, Gaz. méd. de Paris, April, 1860.

19. Toraude, L. G.: Bernard Courtois (1777-1838) et la decouverte de l'iode (1811), Paris, Vigot Frères, 1921.

20. Kimball, O. P.: Differential Diagnosis of Hyperthyroidism, Ohio State M. J. **20**:421, 1924.

cases of toxic goiter—either exophthalmic or toxic adenoma—medication with iodine either ameliorates or aggravates the symptoms, while in simple goiter there is rarely any constitutional effect even with marked shrinkage of the thyroid gland. Marked amelioration or marked aggravation in symptoms after the therapeutic use of iodine may, therefore, be taken as an indication that one is dealing with a toxic goiter. This was well illustrated in cases 3 and 6 of my series. In the former it caused aggravation, in the latter, marked initial improvement. While not an infallible guide, the iodine therapeutic diagnostic test may prove of considerable help in the diagnosis of a doubtful thyrotoxic case.

2. *The Radium Therapeutic Diagnostic Test.*—The application of this test was well brought out in the management of cases 4 and 5 of my series. In both patients with marked toxic symptoms and normal basal metabolic rates radium therapy was followed by marked clinical improvement without any effect on the basal metabolism, except once when it rose temporarily to + 22 at the height of the reaction to radium. Such improvement in toxic cases after the application of radium to the thyroid gland can mean only that the inhibition or arrest of toxic activity of the gland induced by the local application of radium has produced relief of symptoms. Had the toxic symptoms been due to causes residing elsewhere in the body and not in the thyroid gland, no such relief could have been expected. Hence, the radium therapeutic diagnostic test can reasonably be depended on to differentiate a mildly thyrotoxic goiter from such conditions as neurocirculatory asthenia, early questionable tuberculosis, nontoxic goiter, "autonomic imbalance"—when the latter is not merely a manifestation of thyrotoxicosis—etc.

A review of the pediatric literature fails to reveal a single case report in which radium had been used or recommended in the treatment for exophthalmic goiter in children, while several authors did recommend or had carried out surgical intervention in their cases. But is surgical intervention with its attendant mortality rate, even in such prominent thyroid clinics as the Mayo's, the only method of successful local attack on the thyroid gland in the treatment for exophthalmic goiter in childhood? Has radium therapy no record to show of its successful achievements in this disease? I shall briefly recapitulate the history of radium therapy in the treatment for exophthalmic goiter and toxic adenoma of the thyroid as I have done in greater detail in two other studies. Let every unbiased pediatrician carefully weigh the facts and decide in his own mind whether his little patients are to be subjected in the future to the dangers of operative mortality or whether radium is to be given the first choice in the therapeusis of a disease in which surgical intervention does not always cure even if the patient does survive the operation.

The first case of a patient with exophthalmic goiter successfully treated by radium was reported by the prominent surgeon, Abbe,[21] of New York, in 1904. The patient, a poor surgical risk, was refused operation by one of the most eminent surgeons of the time. Following a single interstitial treatment with radium, the patient made a rapid uneventful recovery and had no recurrence during the next twenty-two years, the entire period of observation.

In 1913, Pinch,[22] from the London Radium Institute, reported that four of six patients with exophthalmic goiter who were treated with radium showed improvement.

In 1914, one of the foremost American surgeons,[23] in the course of his Harvey Lecture on "The Rôle of the Thymus in Graves' Disease," cited a case previously thyrodectomized by him.

> The gradual enlargement of two nodules, the remains of the thyroid isthmus . . . had caused the patient great anxiety. . . . Furthermore she experienced a feeling of oppression behind the sternum which had been a constant source of annoyance and occasionally of distress. . . . After a prolonged exposure of the isthmus to 1,300 mgm. of radium, the two nodules vanished promptly and she no longer experienced the feeling of oppression behind the sternum.

The first observer to report a large series of cases of toxic goiter in which the patients were treated by external applications of radium was Aikins[24] of Toronto. During the years 1908 to 1916, he had treated sixteen patients. Two years later, the number grew to forty-five, and in 1920, he was able to report 100 patients treated during a period of twelve years. His results were highly gratifying.

Corroborative of the foregoing were the favorable results achieved by Burrows[25] of Manchester in a series of seventy-nine patients with exophthalmic goiter treated by radium; 80.1 per cent were benefited.

Superior results to the foregoing in the treatment for exophthalmic goiter by radium were obtained by Dawson Turner[26] of Edinburgh. In 1919, Turner reported: "The writer has now treated upwards of fifty cases with radium and with one exception all of those patients derived more or less benefit."

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21. Abbe, R.: Exophthalmic Goiter Reduced by Radium, Arch. Roent. Ray **9**:214 (March) 1905.

22. Pinch, A. F. H.: A Report of the Work Carried Out at the Radium Institute (London) from Jan. 1, 1913, to Dec. 31, 1913.

23. Halstead, W. S.: The Significance of the Thymus Gland in Graves' Disease, Harvey Lecture, March 14, 1914.

24. Aikins, W. H. B.: Radium in Toxic Goiter, Am. J. Roentgenol. **7**:404, 1920.

25. Burrows, A.: Report of Manchester and District Radium Institute from Jan. 1, 1917 to Dec. 31, 1917.

26. Turner, D.: Notes on Radium Treatment, Edinburgh M. J. **22**:79 (Feb.) 1919.

In 1920, Clagett,[27] of Chicago, reported his results in thirty-one patients treated by small doses of filtered radium. Definite improvement was noted in twenty-eight, or 90.3 per cent of the cases. Among these were six recurrent cases after previous thyroidectomies.

In 1921, Terry [28] stated:

> In the treatment of bad risk cases of exophthalmic goiter, it occurred to me that radium emanation could be introduced into the substance of the thyroid under local anesthesia and with a minimum of traumatism. Accordingly Aug. 16, 1920, at the University of California Hospital, I inserted eight tubes of radium emanation, representing ten millicuries in the case of a patient with an extreme degree of hyperthyroidism with exophthalmos.

In 1922, after having treated thirty-three patients by this preliminary introduction of radium emanation prior to thyroidectomy, Terry [29] summarized his observations as follows:

> Having had considerable experience in operating on goiters which had been treated with roentgen rays, we naturally feared that radium emanation might give rise to annoying adhesions between the thyroid and its surrounding structures but we were pleased to find that they were minute points where the needle had entered the gland. . . . . Of the fourteen patients that had resection of the thyroid after the radium treatment four died. . . . In two cases there has been an apparent cure by radium alone. In one the basal metabolic rate was plus 122 per cent before the introduction of . . . the radium emanation. Two months later his basal metabolism was plus 27.5 and four months later it was plus 12.9. The other patient had a basal metabolic rate of plus 84.4 before five tubes of radium . . . were introduced. Two months later his basal metabolism was plus 38 and four months following the radiation it was plus 5.7. He is now working as a stevedore and teamster, and seems entirely recovered.

Loucks [30] declared,

> After seven years of experience, the last three under the most exacting scrutiny by means of laboratory methods and clinical findings, I conclude that toxic goiter can be cured by radium and that it is not a surgical disease. . . . Of the 180 cases treated only four failed to be benefited and died. Three of these were in a state of extremis from myocardial insufficiency and the fourth, an insane patient, died from starvation before the treatment had time to benefit the patient. The remaining 176 or 97.7 per cent were all benefited. In only six of this number was there a second treatment required.

Further detailed reports of the value of radium in the treatment for exophthalmic goiter and toxic adenoma of the thyroid were reported

27. Clagett, A. M.: Radium Therapy of Thyroid, J. Radiol. **1**:121 (Feb.) 1920.

28. Terry, W. J.: Radium Emanation in the Treatment of Goiter, J. A. M. A. **78**:1821 (June 25) 1921.

29. Terry, W. J.: Radium Emanations in Eoxphthalmic Goiter, J. A. M. A. **79**:1 (July 1) 1922.

30. Loucks, R. E.: Pathological Classification of Thyroid Gland Disorders with Radium Treatment in Toxic Goiter, Am. J. Roentgenol. **8**:755 (Dec.) 1921.

by Grier,[31] Hagans,[32] Butler,[33] Gudzent,[34] Larkin,[35] Loucks,[36] Ginsburg and others.

CONCLUSIONS

1. Thyrotoxicosis—toxic or exophthalmic goiter—is a disease which affects persons of all ages, from budding infancy to withering old age. Even the new-born infant has not escaped this affliction.[37]

2. Although of decidedly less frequent occurrence than in adult life, thyrotoxicosis in childhood, especially in its formes frustes, is by no means as rare a disease as the medical literature would lead one to believe.

3. Thyrotoxicosis in childhood, although generally milder and therefore more atypical in its manifestations than in the adult, may nevertheless run an acute course with fatal issue.

4. Although the classic type with fully developed cardinal signs presents no difficulty in diagnosis, the atypical forms, especially those with low basal metabolic rates, do present great diagnostic difficulty at times.

5. When the clinical symptoms and signs supplemented by laboratory studies are not decisive in differentiating a simple from a toxic goiter, the iodine and the radium therapeutic diagnostic test may be greatly helpful in eliciting a correct diagnosis.

6. Although some children suffering from thyrotoxicosis—toxic adenomatous or exophthalmic goiter—have recovered under medical treatment alone, many have not. In Sattler's series of sixty-two medically treated patients, 9.68 per cent died as the result of the disease; 19.35 per cent were only slightly improved; 6.4 per cent moderately improved; 33.8 per cent markedly improved, and only nineteen, or 30.64 per cent, were considered cured.

7. Surgical intervention in exophthalmic goiter is not always curative. Thyroidectomy even in the hands of an expert surgeon may fail,

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31. Grier, G. W.: X-Ray and Radium Treatment of Goiter, Atlantic M. J. **26**:516 (May) 1923.

32. Hagans, F. M.: Radium Therapy of Thyroid, Endocrinology **8**:404 (May) 1924.

33. Butler, C.: Radium Treatment of Exophthalmic Goiter (Uruguay), Ann. de Fac. de Montevideo **8**:793 (Sept.) 1923.

34. Gudzent, F.: Ueber die Einwirkung kleiner Strahlendosen (Radium und Mesothorium) auf die Thyreotoxikosen und den Basedow, Klin. Wchnschr. **3**: 2329 (Dec. 16) 1924.

35. Larkin, A. J.: Radium in Twenty Cases of Hyperthyroidism, Illinois M. J. **49**:468, 1926.

36. Loucks, R. E.: Clinical Evidence of Thyrotoxic Control After Radium Therapy, Am. J. Roentgenol. **18**:509, 1927.

37. White, C.: A Foetus with Congenital Hereditary Graves' Disease, J. Obst. & Gynec. Brit. Emp. **21**:231, 1912.

as in the only case of my series, case 4, in which surgical intervention was resorted to before treatment with radium.

8. Surgical intervention, even the most expert at the Mayo Clinic, fortified even by the preoperative administration of a compound solution of iodine, carries with it a mortality rate in exophthalmic goiter in children. In Helmholz's recent report from the Mayo Clinic two of twenty-four children on whom operations were performed lost their lives as the result of the operation. This gives a mortality rate of 8.33 per cent, which is almost as high as that for medical treatment alone in Sattler's series.

9. Surgical intervention is no longer the only method of successful local attack on the thyroid gland in the treatment for thyrotoxicosis, either toxic adenomatous or exophthalmic goiter.

10. Radium therapy efficiently used offers a safe, dependable, bloodless method that can yield as brilliant results as surgical operation, if not more brilliant, without its attendant mortality.

TRACHEOBRONCHIAL DIPHTHERIA

A REPORT OF TWENTY-FOUR CASES *

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General textbooks of medicine as well as current medical literature contain rather meager reference to the malignant form of diphtheria which involves the trachea and the bronchi. Osler's "System of Medicine" refers to the condition as being "extremely rare," and this seems to be the prevailing opinion. That tracheobronchial diphtheria, however, is not an uncommon occurrence is evidenced by the fact that during a period of eighteen months, twenty-four patients with this disease were admitted to the Municipal Contagious Disease Hospital, and that deaths due to tracheobronchial diphtheria formed 11 per cent of all deaths from diphtheria in this hospital during the same period. As this type of diphtheria has received scant attention in pediatric medical literature and as its early recognition and treatment are so important, these twenty-four cases are reported.

Lynah [1] described two types of cases: one in which the membrane formed in the smaller bronchi and extended upward into the trachea; the other type in which the membrane formed above and spread downward into the bronchi. Lynah found intubation and tracheotomy equally unsuccessful in the treatment and reported a recovery of 64 per cent of cases following bronchoscopy with suction for the mechanical removal of the obstructing membrane. Smith [2] reported one case in which the patient recovered after coughing up a membranous cast of the trachea and bronchi. Dupuy [3] reported three cases in which the condition was diagnosed by laryngoscopic examination. Boebinger [4] described three cases and recommended the treatment advocated by Lynah. Carpenter [5] reported a case in which the patient died from

* Submitted for publication, Nov. 3, 1928.

* From the Municipal Contagious Disease Hospital, Department of Health, Chicago.

1. Lynah, H. L.: Treatment of Diphtheria of the Tracheobronchial Tree, Laryngoscope **26**:158, 1916.

2. Smith, M.: Cast of Primary Tracheal or Bronchial Diphtheria, Brit. M. J. **2**:57, 1925.

3. Dupuy, H.: Tracheobronchial Diphtheria, New Orleans M. & S. J. **76**:113 (Sept.) 1923; South. M. J. **15**:321, 1922.

4. Boebinger, M. P.: Tracheobronchial Diphtheria, New Orleans M. & S. J. **78**:84 (Aug.) 1925.

5. Carpenter, E. W.: Diphtheria of Fauces, Larynx, Trachea and Bronchi, J. South Carolina M. A. **15**:404, 1919.

toxemia several hours after a successful bronchoscopy with aspiration had been performed. Jackson [6] emphasized the value of bronchoscopy in the treatment and prevention of massive collapse of the lung due to "obstructing diphtheritic exudates."

CASE HISTORIES

The histories obtained in this group of cases were so variable and unreliable that they were of little assistance in making a diagnosis. All of the patients were children varying in age from 1 to 10 years. Cough was frequently the first symptom complained of, leading to a diagnosis of "bronchitis" or "a cold" during the first few days of illness. During this time also, tiredness and lack of desire to play were sometimes complained of. Not until the onset of dyspnea was the condition of the patients considered serious enough to require medical or hospital care. Three of the patients gave a history of measles with an onset from one to two weeks prior to admission, and in each one of these there was evidence of a fading rash. These three patients had been treated for bronchitis until obstructive respiratory symptoms appeared. In the twenty-four cases reported, the duration of the illness, prior to admission to the hospital, varied from four to ten days, the average being five and one-half days, according to the history obtained. The actual duration was probably one or two days longer. In no instance had diphtheria antitoxin been administered previous to the date of admission to the hospital. In view of this fact, it is not surprising that there was only one recovery in this group.

SIGNS AND SYMPTOMS

So distinctive are the signs and symptoms of tracheobronchial diphtheria that a careful physical examination rarely fails to reveal a correct diagnosis. These patients appear extremely toxic, with a temperature ranging from 102 to 105 F. The face has a pronounced pallor and a waxy appearance. Cyanosis of the lips and finger-nails is usually present. The tonsils and pharynx are covered with a thick membrane in some of the patients; in others, the fauces are entirely free from membrane. The voice is somewhat hoarse, except when there is laryngeal involvement, in which case aphonia is always present. Severe dyspnea, which is a constant observation in all cases, tends to be progressive rather than paroxysmal. Marked retraction of the intercostal spaces and of the epigastric region occurs. This type of retraction forms an important differentiation from laryngeal diphtheria, which is

6. Jackson, Chevalier: Bronchoscopy and Eosophagoscopy, ed. 2, Philadelphia, W. B. Saunders Company, 1927, p. 301. Jackson, Chevalier, and Lee, Walter Estell: Acute Massive Collapse of the Lungs, Ann. Surg. **82**:364 (Sept.) 1925.

Reports from Cases of Tracheobronchial Diphtheria

Case	Name	Age	Days Sick Prior to Receiving Antitoxin	Days Sick Prior to Admission to Hospital	Tonsillar Membrane	Nasal Membrane	Temperature	Pulse	Respiration	Time of Death After Admission to Hospital	Amount of Antitoxin Units	History of Measles Immediately Preceding	Culture Report from Nose and Throat	Chest	Autopsy Observations
1	M. R.	5	6	6	0	0	104	140	50	24 hours	10,000	+	+	Intercostal retraction, râles, hyperresonance	Membranous cast of tracheobronchi, myocarditis
2	R. L.	5	No antitoxin	4	0	0		Died in receiving room				+	+	Marked intercostal retraction.....	Cast of trachea and bronchi, heart and liver large, myocarditis
3	L. K.	8	4	4	+	+	103	140	40	3 days	40,000	0	+	Intercostal retraction, suppression breath sounds, râles	Membranous cast of larynx, tracheobronchi, atelectasis, myocarditis of the right side of the left lung
4	G. J.	2½	10	10	+	+ hemorrhage	104	148	48	10 hours	40,000	0	+	Bronchial breathing, dulness of lower lobes, terminal bronchial pneumonia	Membranous cast of tracheobronchi, consolidation of both lower lobes
5	S. N.	2	4	4	0	0	102.2	152	42	48 hours	20,000	0	+	Suppression of breath sounds, intercostal retraction	Membranous cast, beginning bronchopneumonia, liver congested, heart normal
6	M. R.	3½	5	5	0	0	103	128	28	7 days	20,000	+	+	Intercostal retraction, suppression of breath sounds, hyperresonance	Membrane of trachea and main bronchi, bronchopneumonia, myocarditis, hepatitis
7	A. T.	1	4	4	+	+	103	156	32	48 hours	30,000	0	+	Intercostal retraction, râles, suppression at bases	Membrane of larynx, tracheobronchi and upper two thirds of esophagus, myocarditis
8	S. L.	7	No antitoxin	7	+	+		Died in receiving room				0	+	Asphyxia	Cast of trachea and left bronchus, myocarditis, petechial hemorrhages
9	E. G.	8	No antitoxin	7	+	+		Died in receiving room				0	+	Marked retraction, pneumonia of right side of lung, hyperresonance of left	Membrane of larynx, trachea and right bronchus, consolidation right middle lobe
10	G. F.	4	2(?)	2	+	+	103	160	40	3 days	40,000	0	+	Moist râles, areas of emphysema, hyperresonance	Membrane of larynx, trachea, bronchi, hemorrhages of pleura and pericardium

11	E. M.	10	7	7	0	0	104	140	30	29 days	40,000	0	+	Intercostal retraction, râles, suppression of breath sounds, coughed up cast of trachea and bronchi	Recovery
12	P. M.	5	5	5	+	+		Died in receiving room, tracheotomy prior				0	+	Intercostal retraction	Membrane of tracheobronchi, myocarditis
13	D. R.	10	?	?	+	+	105	140	40	12 hours	50,000	0	+	Intercostal and epigastric retraction, moist râles	Membrane in trachea and right main bronchus, petechial hemorrhages
14	C. R.	1	4	4	0	0	105	160	60	30 hours	20,000	0	+	Shallow respiration, bronchial breathing, dulness	Tracheobronchial membrane, purulent bronchitis, heart normal, liver congested, large
15	G. V.	2	6	6	0	0	102.6	140	38	3 days	40,000	0	Negative	Marked retraction, hyperresonance, râles	Tracheobronchial membrane, terminal bronchopneumonia, myocarditis
16	S. Z.	2½	5	5	+	+	103.4	170	44	2 days	40,000	0	+	Suppression of breath sounds, râles, intercostal retraction	Tracheobronchial membrane, hemorrheages into pleura, myocarditis
17	J. M.	2	5	5	0	0	104.6	156	72	26 hours	20,000	0	Negative	Intercostal breathing, râles resonant, suppression	Tracheobronchial membrane, atelectasis of left upper lobe (fig. 3)
18	J. B.	2	6	6	+	0	102	160	24	5 hours	40,000	0	+	Intercostal retraction, râles subcrepitant, suppressed breathing	Tracheobronchial membrane, early bronchopneumonia, hemorrhages of pericardium
19	D. B.	5	5	5	+	+ hemorrhage	101	148	52	8 hours	40,000	0	+	Intercostal retraction, râles in bronchi, suppression	Petechial hemorrhages, emphysema, cast of tracheobronchi, myocarditis
20	C. P.	6	3	3	+	+	102	140	36	2 days	40,000	0	+	Intercostal and epigastric retraction, suppression of breath sounds	Tracheobronchial membrane, atelectasis
21	B. B.	5	6	6	0	+		Died in receiving room				0	+	Intercostal retraction	Cast of trachea and bronchi, emphysema, myocarditis
22	G. K.	9	4	4	+	0	101	140	28	8 hours	40,000	0	+	Marked retraction, râles, hyperresonance	Tracheobronchial membrane, edema of neck and chest, myocarditis
23	F. S.	4	4	4	+	+ hemorrhage	104	140	68	17 hours	30,000	0	+	Intercostal retraction, râles moist, suppression of breath sounds	Tracheobronchial membrane, atelectasis, hemorrhagic suprarenals
24	R. B.	5	8	8	+	+ hemorrhagic	...	...	..	2 hours	40,000	0	+	Retraction entirely intercostal, hyperresonance, râles	Tracheobronchial membrane, atelectasis, myocarditis, hemorrhages

characterized by recession of the suprasternal, supraclavicular and infraclavicular spaces. Not infrequently paroxysms of coughing occur during which the patient may cough up pieces of membrane or even a complete membranous cast of the tracheobronchial tree. Hemorrhages in the form of petechiae frequently occur into the skin or from the mucous membranes of the nose and throat.

Fig. 1.—Tracheobronchial diphtheritic membrane.

Auscultation and percussion reveal somewhat constant observations in tracheobronchial diphtheria; these changes are not unlike those produced by a foreign body in the bronchus. There is suppression of breathing over the entire chest, with breath sounds almost absent at the bases of the lungs. When only one side of the chest is involved, there is harsh emphysematous breathing over the unaffected side. Occasionally, the to-and-from flapping sound of a loose piece of membrane may be heard. Showers of moist râles are heard over the whole chest, but

occasionally these râles may be subcrepitant. The percussion note is usually hyperresonant because of the extensive emphysema or because of a lung distended with air which is unable to escape. The dulness due to atelectasis which is a frequent observation at autopsy is completely masked by the emphysema.

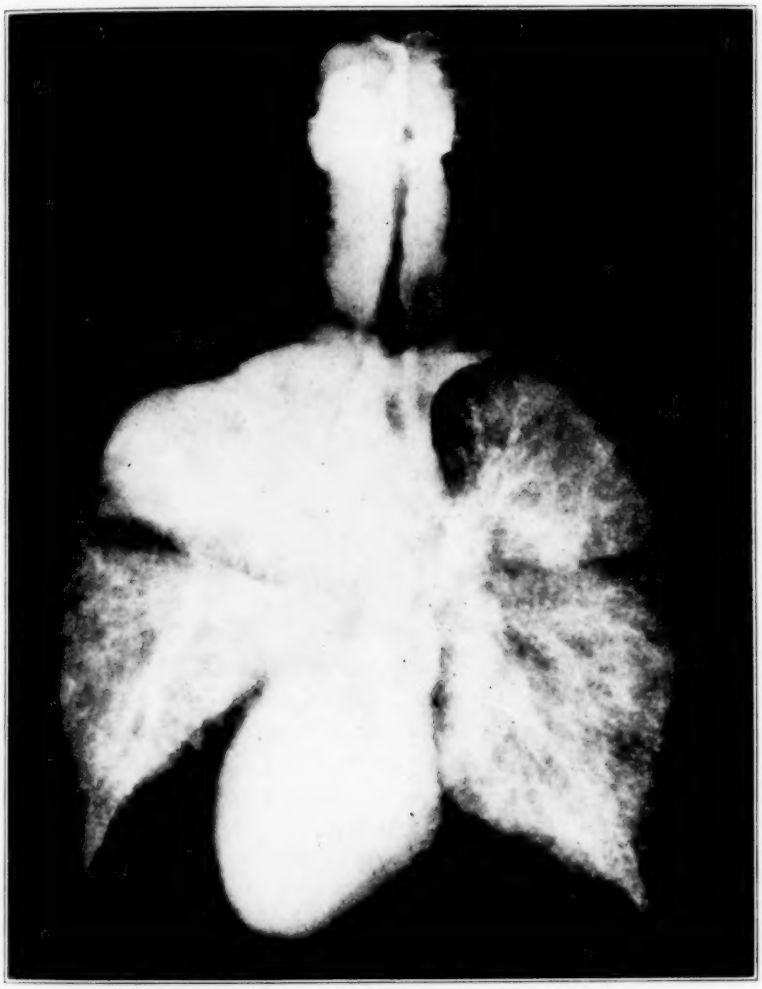

Fig. 2.—X-ray picture taken at autopsy, showing massive collapse of the upper lobe of the left lung in a patient with tracheobronchial diphtheria.

X-ray pictures do not cast a shadow of a bronchial diphtheritic membrane. This examination, however, is of value and interest in cases in which the obstructing membrane has produced atelectasis or massive collapse of the lung (fig. 2). The roentgenograms may closely

simulate those obtained when there is a foreign body in a bronchus with a massive collapse. In these cases the heart is drawn over toward the affected side.

Cases of tracheobronchial diphtheria in which there is no evidence of faucial or nasal involvement at times present some difficulty in diagnosis. The conditions requiring differentiation are: laryngeal diphtheria, the presence of a foreign body, bronchial asthma, bronchopneumonia, edema of the larynx and enlargement of the thymus. Laryngeal diphtheria is characterized by aphonia, suprasternal, supraclavicular and infraclavicular retraction and spectacular response to intubation. In tracheobronchial diphtheria, the voice is retained but is usually horase; the retraction is most marked in the intercostal and epigastric regions; there is no response to intubation, and the patient is extremely toxic. The symptoms in cases in which a foreign body is present usually have an acute onset, in which the history of a sudden coughing and choking attack is frequently obtained. The roentgen examination may be of assistance if the foreign body is opaque. In asthma, the expiratory excursion is prolonged and difficult; there is usually the history of previous attacks; the wheezy respiratory sounds are characteristic, and eosinophilia may be present. Edema of the larynx has a sudden onset and is characterized by loss of voice and rapidly increasing dyspnea with asphyxiation within a few hours. Tracheobronchial diphtheria is frequently wrongly diagnosed as bronchopneumonia. Dulness, however, is usually absent for obvious reasons to which I have already referred.

PATHOLOGY

Autopsies were performed in twenty-two cases. In nine of these, there was no faucial involvement, the infection being primary in the trachea or bronchi. In five cases, death was due to asphyxia, caused by complete obstruction at or just below the bifurcation of the trachea. In the remainder, death was attributed to toxemia and myocardial failure. A membrane involving the trachea, bronchi and smaller bronchioles was found in every case. In some cases areas of beginning necrosis of the membrane with considerable purulent secretion into the bronchi were shown. In three instances, the membrane was confined to the trachea and to the right side of the chest, the left side being entirely free. Emphysema and petechial hemorrhages were frequently found over the surface of the lungs. In some, a massive collapse of a whole lobe of the lung was present, while in others the atelectasis was confined to smaller areas. Evidences of beginning bronchopneumonia were found in seven cases. The pathologic processes referable to the heart were characterized by enlargement, extensive parenchymatous degeneration and hemorrhages into the pericardium

and myocardium. The liver was consistently enlarged and congested, with marked evidences of toxic changes. The kidneys showed marked cloudy swelling. In almost every case the suprarenal glands were found to be hemorrhagic, the hemorrhages not infrequently extending into the perisuprarenal tissues.

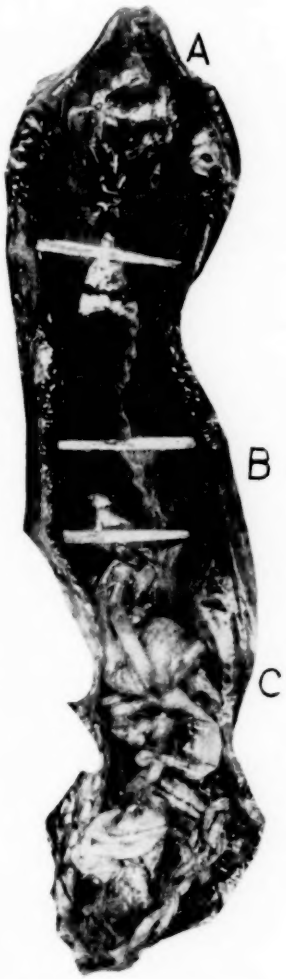

Fig. 3.—Trachea showing diphtheria membrane which caused complete obstruction at the bifurcation. *A* represents the epiglottis; *B*, the trachea and *C*, the membrane.

TREATMENT

Large doses of diphtheria antitoxin (from 40,000 to 50,000 units) were given to each patient on admission to the hospital. Trial intubation, which was performed in every case, occasionally gave temporary

relief, but as a rule it failed to relieve the dyspnea. In two cases the intubation tube pushed the membrane toward the bifurcation, which produced complete obstruction and asphyxia (fig. 3). Tracheotomy was performed in three cases and was equally unsuccessful. In patients in whom the condition has been diagnosed during the first four or five days of illness before the onset of myocardial failure, and who have not responded to trial intubation, bronchoscopy with aspiration by a competent bronchoscopist undoubtedly offers the only chance of combating this type of obstruction. Because of the extremely toxic and, in some instances, moribund condition of this group of patients with rapidly failing hearts, bronchoscopy seemed to be definitely contraindicated and was not performed. In patients in whom the condition is of more than five or six days' duration with extensive diphtheritic involvement, it is doubtful that any amount of antitoxin or any operative measures have any effect.

SUMMARY

Twenty-four cases of tracheobronchial diphtheria are reported with the clinical and pathologic observations.

The most distinctive clinical features of the condition were severe toxemia, marked intercostal and epigastric reactions, retention of voice, suppression of breath sounds and hyperresonance.

The differential diagnosis from laryngeal diphtheria, foreign body, asthma, bronchopneumonia and edema of the larynx is outlined.

Autopsies performed in twenty-two cases showed atelectasis caused by membranous obstruction to be a frequent occurrence.

Large doses of diphtheria antitoxin are desirable. Bronchoscopy with aspiration is indicated if performed before the onset of myocardial failure.

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THE RELATIONSHIP BETWEEN FIBRIN CONTENT AND SEDIMENTATION INDEX IN ORTHOPEDIC CASES *

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AND

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MINNEAPOLIS

In order to facilitate comparison with previous work,[1] the children chosen for this study were between 7 and 17 years of age. Fifty of each sex were chosen. All of the boys and forty-two of the girls were patients in Gillette Hospital; the remaining eight girls were patients in Shriners' Hospital.

The blood was drawn by venipuncture about two hours after breakfast. The sedimentation rate was determined by the Cutler graphic method,[2] 0.5 cc. of oxalate instead of citrate being used. Readings were taken at intervals of fifteen, thirty, forty-five and sixty minutes. The fibrin was determined in duplicate by the Wu [3] colorimetric method, the precautions mentioned in earlier papers being observed.

The average sedimentation index (one hour reading) was 12.58 $\pm$ 0.83 mm. for the boys and 12.64 $\pm$ 0.67 mm. for the girls. The difference between the sexes is 0.06 $\pm$ 1.06 mm., which is not significant. In the thirty boys from Lymanhurst,[1] who were between 7 and 17 years of age, the average index was 6.60 $\pm$ 0.40 mm.; for the twenty-four girls it was 6.50 $\pm$ 0.44 mm. The difference between the sexes is 0.10 $\pm$ 0.59 mm., which is likewise insignificant. Thus, in children between 7 and 17 years of age there is not any significant difference in sedimentation rate between the sexes. This fact applies to orthopedic cases chosen at random and to undernourished children who were kept under observa-

* Submited for publication, Nov. 30, 1928.

* From the Department of Physiology, The University of Minnesota, Gillette State Hospital for Crippled Children and Shriners' Hospital for Crippled Children.

1. Greisheimer, Esther M.; Johnson, Olga H., and Ryan, Mary: The Relationship Between Sedimentation Index and Fibrin Content in Relatively Normal Individuals, Am. J. M. Sc., to be published.

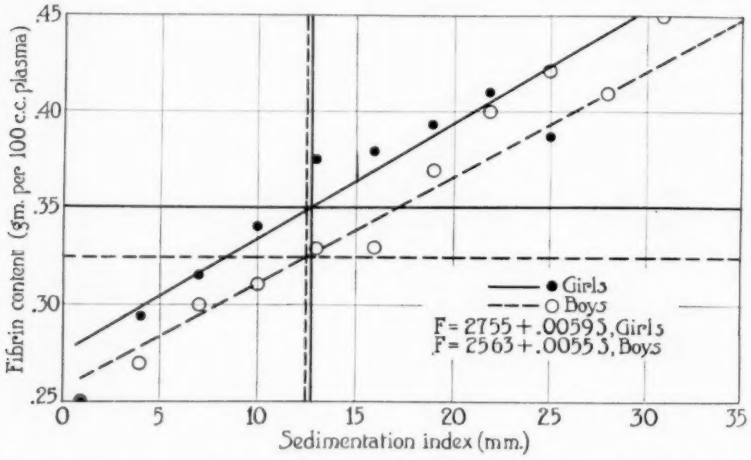
2. Cutler, J.: The Graphic Presentation of the Blood Sedimentation Test, Am. J. M. Sc. **171**:882, 1926.

3. Wu, H.: Colorimetric Method for the Determination of Fibrinogen, J. Biol. Chem. **51**:53, 1922.

tion because of hilum tuberculosis or exposure to open cases (Lymanhurst). The rate is faster in the orthopedic groups, as would be expected.

The average fibrin content for the orthopedic boys was 0.3250 ± 0.0056 Gm. per hundred cubic centimeters of plasma. For the girls it was 0.3500 ± 0.0060 Gm. The difference between the sexes is 0.0250 ± 0.0082 Gm., which may be statistically significant. The boys from Lymanhurst had an average of 0.3183 ± 0.0063 Gm., and the girls had an average of 0.3021 ± 0.0037 Gm. The difference is 0.0162 ± 0.0073 Gm., which is probably not significant. The fibrin content is slightly higher in the orthopedic group.

The correlation coefficient, r_{FS}, between the fibrin content and the sedimentation index was 0.757 ± 0.041 for the boys. (F = grams of



The empiric mean fibrin values found for each sedimentation index. The agreement between these means and the regression lines (calculated from the means, standard deviations and correlation coefficient) is satisfactory, considering the number of cases.

fibrin per hundred cubic centimeters of plasma, and S = sedimentation index in millimeters.) This is 18.4 times as large as its probable error. The linear regression equation is F = 0.2563 + 0.0055 S; when, as in the foregoing correlation, F = grams of fibrin per hundred cubic centimeters of plasma, and S = sedimentation index in millimeters. The empiric mean fibrin values as ordinates are plotted against the indexes in the accompanying chart.

The correlation coefficient, r_{FS}, was 0.714 ± 0.047 for the girls, which is 15.2 times as large as its probable error. The linear regression equation is F = 0.2755 + 0.0059 S. The actual means and the fitted regression line are shown in the chart.

The difference between the correlation coefficients for the two sexes is 0.043 ± 0.062. Thus, the agreement between the correlations for

fibrin content and sedimentation rate is excellent in the two sexes in the orthopedic group. In the Lymanhurst group, the correlation coefficient was 0.497 ± 0.093 for the boys, and 0.374 ± 0.118 for the girls. The orthopedic group shows a higher correlation.

The table presents the diagnosis, the number of cases, the sex, the sedimentation index and the fibrin content of the orthopedic group. For convenience, the list is arranged according to the rapidity of sedimentation, as given by the index.

Observations on Sedimentation Index and Fibrin Content of the Orthopedic Group

Diagnosis	Number of Cases	Sex	Sedimentation Index, Mm.	Per Cent of Fibrin
Congenital torticollis	1	F	2	0.253
Traumatic paralysis	1	M	3	0.256
Hypospadias	1	M	3	0.208
Tertiary repair—cleft palate	1	F	4	0.294
Old unrecognized fracture	1	F	5	0.311
Rickets	1	M	6	0.294
Idiopathic scoliosis	2	M	7.5	0.300
Nonsuppurative arthritis	1	F	8.0	0.331
Acute nonsuppurative infection	1	M	8.0	0.274
Bowing of extremities	1	F	8.0	0.364
Club foot	1	F	9.0	0.304
Hemophilia	1	M	9.0	0.325
Anterior poliomyelitis	15	M	9.13	0.311
Anterior poliomyelitis	15	F	9.25	0.312
Malunited fracture	1	M	10.0	0.290
Congenital dislocation of hip	1	M	10.0	0.328
Idiopathic scoliosis	5	F	10.6	0.352
Spastic paraplegia	1	F	11.0	0.333
Infectious arthritis	1	F	12.0	0.387
Congenital dislocation of hip	7	F	12.1	0.337
Spastic paraplegia	3	M	12.6	0.328
Tuberculosis of the bone	9	M	14.1	0.329
Tuberculosis of the bone	7	F	14.5	0.381
Old infection	6	M	15.8	0.332
Subacute suppurative arthritis	1	F	18.0	0.433
Chronic osteomyelitis	5	M	19.4	0.386
Osteogenesis imperfecta	2	F	19.5	0.373
Chronic osteomyelitis	5	F	20.6	0.406
Traumatic hip	2	M	21.0	0.376
Subacute osteomyelitis	3	F	21.7	0.351
Acute osteomyelitis	1	M	30.0	0.466

SUMMARY AND CONCLUSIONS

1. These studies were made on the venous blood of children. The average sedimentation index (one hour reading by the Cutler graphic method) for fifty boys between 7 and 17 years of age requiring orthopedic treatment was 12.58 ± 0.83 mm.; for fifty girls, it was 12.64 ± 0.67 mm. The difference between the sexes is 0.06 ± 1.06 mm. The rate is faster in these children than in the Lymanhurst group of undernourished children who were under observation because of hilum tuberculosis or exposure to open cases.[1] In both groups, an insignificant sexual difference exists. In adults, under similar conditions, the rate

is invariably faster in women than in men. Apparently some change occurs at the age of puberty or shortly thereafter which is responsible for the sexual differentiation in cases of adults. This point needs further study.

2. The average fibrin content for the boys requiring orthopedic treatment was 0.3250 ± 0.0056 Gm. per hundred cubic centimeters of plasma (by the Wu colorimetric method); for the girls, it was 0.3500 ± 0.0060 Gm. The difference between the sexes is 0.0250 ± 0.0082 Gm., which may be statistically significant. In the Lymanhurst group, a fibrin content lower than this was found in both sexes.

3. The correlation coefficient, r_{FS}, between the fibrin content and the sedimentation index was 0.757 ± 0.041 for the boys, and 0.714 ± 0.047 for the girls. Both are clearly significant. The degree of correlation was higher in the orthopedic group than in the Lymanhurst group.

IMMUNIZATION WITH MODIFIED TOXIN *

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The introduction by Park [1] of the 0.1 L + diphtheria toxin-antitoxin mixture seems to have done away with the possibility of its inducing human hypersensitiveness [2] to horse serum. Indeed, Bauer and Wilmer [3] concluded that hypersensitivity to horse protein is not developed with this mixture; more recently, Spicer [4] concluded that previous administration of toxin-antitoxin has little if any effect on subsequent treatment with serum and that the danger of sensitization is greatly exaggerated. On the other hand, Stewart,[5] Gatewood and Baldridge [6] and Lathrop [7] reported instances of sensitization to horse serum after injections of toxin-antitoxin, although no evidence is presented that the hypersensitiveness was not present before the administration of the toxin-antitoxin.

The possibility of sensitization has led Hooker [8] to suggest the use of goat serum in the preparation of toxin-antitoxin, and has given

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* From the Department of Pediatrics, College of Medicine, Syracuse University and from the Syracuse Health Department and Health Demonstration.

* Read before the Western New York Branch of the Society for Experimental Biology and Medicine at Rochester, N. Y., May 12, 1928, and since revised for publication.

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2. Longcope, W. T., and Rackemann, F. M.: The Relation of Circulating Antibodies to Serum Disease, J. Exper. Med. **27**:341, 1918. Park, W. H.: Human Hypersensitiveness to Whole Horse Serum or Serum Globulin Following Diphtheria Toxin-Antitoxin Injections: Its Importance, J. Immunol. **9**:17, 1924. Hooker, S. B.: Human Hypersensitiveness Induced by Very Small Amounts of Horse Serum, J. Immunol. **9**:7, 1924.

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4. Spicer, Sophie: The Effect of Previous Administration of Antitoxin and Toxin-Antitoxin on Serum Reaction, J. A. M. A. **90**:1778 (June 2) 1928.

5. Stewart, C. A.: Anaphylactic Reactions Following Administration of Serums to Children Previously Immunized Against Diphtheria, J. A. M. A. **86**: 113 (Jan. 9) 1926; Serum Sensitization Resulting from Diphtheria Administration, J. A. M. A. **88**:1220 (April 16) 1927.

6. Gatewood, W. E., and Baldridge, C. W.: Tissue Hypersensitiveness Following the Administration of Toxin-Antitoxin, J. A. M. A. **88**:1068 (April 2) 1927.

7. Lathrop, F. W.: Sensitization to Horse Serum Following Toxin-Antitoxin Injection, J. A. M. A. **89**:1602 (Nov. 5) 1927.

8. Hooker (footnote 2, third reference).

impetus to the use of detoxified toxins. In 1924, Ramon [9] introduced the term anatoxin to describe diphtheria toxin which has completely lost its toxicity through the action of formaldehyde and heat, but which has retained its antigenic power. This atoxic diphtheria toxin is known in English speaking countries as toxoid,[10] and is now being largely used in Canada. The term is also applied to toxin modified after the method of Ramon but without complete detoxication. Larson has introduced toxin detoxified with sodium ricinoleate and has made use of such toxins in immunizing persons against diphtheria and scarlet fever.[11]

TESTS WITH TOXINS DETOXIFIED WITH SODIUM RICINOLEATE

Early in 1927, Professor Larson of the University of Minnesota sent me a supply of combined scarlet fever and diphtheria vaccine which had been detoxified with sodium ricinoleate. Each cubic centimeter contained 0.1 L + diphtheria toxin and a culture of the scarlet fever streptococcus containing 3,000 skin test units. The instructions were to keep this material at a temperature not lower than 50 F. and to consider thirty days as the expiration time. It was recommended to give children three injections of 1 cc. each at an interval of from two to four weeks. With this material it had been found, after the completion of 6,000 inoculations in Minneapolis, that there was an incidence of 0.83 cases per thousand among the vaccinated as against 8.3 cases per thousand among the unvaccinated children.[12]

The ricinoleated vaccine was given to a small group of children, and the results were controlled by making Dick and Schick tests before and after the injections. It was desired to repeat the tests at various intervals, but this was not found practicable with small children in private homes, and many of the institutional children had left when the time for the retests came. For the tests, Schick and Dick outfits supplied by the New York State Laboratory were used in accordance with the accompanying instructions. The reactions were measured and read off to a clerk; an attempt was not made to record accurately the amount of infiltration.

About twenty-five children were given the Schick and Dick tests, followed by the injections of the ricinoleated vaccine. Only seventeen

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9. Ramon, G.: Sur l'anatoxine diphtérique et sur les anatoxines en général, Ann. de l'inst. Pasteur **29**:1, 1925.

10. Fitzgerald, J. G.: Diphtheria Toxoid as an Immunizing Agent, Ann. Clin. Med. **5**:870, 1927.

11. Larson, W. P., and Eder, H.: Immunization Against Diphtheria with Toxin Detoxified with Sodium Ricinoleate, J. A. M. A. **86**:998, 1926. Larson, W. P.; Huenekens, E. J., and Colby, W.: Immunization Against Scarlet Fever with Toxin Detoxified with Sodium Ricinoleate, J. A. M. A. **86**:1000, 1926.

12. Larson, W. P.: Personal communication to the author, Feb. 10, 1927.

were retested by the end of ten months. Table 1 gives the results of the tests on seventeen children ranging in age from 1 to 10 years. Two of these children received only two doses each two weeks apart. Only four children showed reactions, the local erythema measuring from about 2 to 5 cm. in diameter. All showed positive reactions to the Dick test and all but three positive reactions to the Schick test prior to the injections. In eight children the Dick test was repeated within three months of the injections. In all children, the Schick and Dick tests were repeated after from eight to ten months.

For simplification in the analysis of the table, certain rather arbitary standards might well be utilized. In this study, a reaction to the

TABLE 1.—*Results of Dick and Schick Tests Before and After Administration of Ricinoleated Vaccine*

			Primary Tests		Secondary Tests		
Case	Age	Sex	Schick 12/14/26	Dick 12/14/26	Dick Retest 3 Months Later	Dick Retest 8 to 10 Mos. Later	Schick Retest 8 to 10 Mos. Later
C. D.	2	M	1.2 × 1	1.5 × 1.0	Negative	1.0 × 1.0	1.0 × 1.0
K. F.*	2	F	0.5 × 0.5	3.0 × 3.0	2.0 × 1.5	2.0 × 2.0§	Negative
G. R.†	2	M	1.0 × 1.0	1.5 × 1.5	0.5 × 0.5	1.2 × 1.0	1.0 × 0.8
C. B.	3	F	0.3 × 0.4	1.0 × 1.0	1.0 × 1.0§	Negative	Negative
D. J.‡	2	M	Negative	1.5 × 1.5	1.5 × 1.0§	1.5 × 1.6	Negative
R. H.	4	F	1.0 × 1.0	3.0 × 3.0	1.0 × 0.5	1.4 × 1.2§	Negative
M. E.	10	F	Negative	2.0 × 1.5	3.0 × 2.0	2.2 × 1.5	Negative
B. J. B.	2	F	2.0 × 2.0	2.5 × 2.5	1.5 × 1	Negative	2.0 × 1.5
P. W.	2	F	0.5 × 0.6	1.5 × 1.0	Not done	1.0 × 1.0	0.5 × 0.6
D. K.‖	5	M	1.0 × 1.0	2.0 × 1.0	Not done	2.0 × 1.6§	Negative
H. S.	8	F	2.0 × 1.5	1.5 × 1.5	Not done	1.5 × 2.0§	1.6 × 1.2§
J. S.	5	F	2.0 × 1.5	1.5 × 1.3	Not done	2.0 × 2.0**	1.6 × 1.2
A. Y.	6	M	Negative	2.3 × 1.5	Not done	2.3 × 1.3§	Not done
A. S.#	7	F	0.5 × 0.7	1.5 × 2.0	Not done	1.5 × 1.4§	Negative
A. W.	6	M	1.0 × 0.8	3.0 × 2.0	Not done	2.0 × 1.0	Negative
P. M.¶	1	F	0.4 × 0.2	1.5 × 1.0	Not done	0.6 × 0.8	Negative
R. G.¶	2	F	1.0 × 1.0	1.0 × 1.5	Not done	1.2 × 1.5	1.0 × 1.0

* Slight reaction after first dose; immediate reaction after third dose.
† Local reaction 5 cm. in diameter after second dose.
‡ Slight reaction after first dose.
‖ Developed scarlet fever—onset 3/10/28.
Local reaction 1 × 2 cm. after first dose.
¶ Had only two doses.
§ Infiltration reduced.
** Control 0.5 × 0.5 cm.

Schick test that is no larger than 0.5 cm. in one diameter, is considered slightly positive; from 0.5 to 1 cm. moderately positive, and over 1 cm. markedly positive. Similarly, a reaction to the Dick test 1 cm. in one diameter is slightly positive; over 1 cm. and up to 2 is moderately positive, and over 2 cm. markedly positive. On the retest either test reaction was considered slightly reduced when one diameter was lessened by 0.5 cm., moderately reduced when it was lessened by 1 cm. and markedly reduced when it was lessened by 2 cm.

When table 1 is scrutinized on this basis, it is found that only one child (C. B.) who gave slightly positive reactions to the Schick and Dick tests later gave negative reactions to both. Of the thirteen other children who gave positive reactions to the Schick test, six later gave

negative reactions. Four of these gave moderately positive and two slightly positive reactions prior to the injections. Three markedly positive reactions to the Schick test became slightly reduced. In four cases the reactions were unchanged, one being slightly positive, one markedly and two moderately.

Of the sixteen other children who gave positive reactions to the Dick test, only one who had a markedly positive reaction later gave a negative reaction. Eight of the reactions were reduced in size: of these, five moderately positive reactions were slightly reduced and three markedly positive reactions moderately reduced. Four—three moderately and one markedly positive reactions—were unchanged, and three moderately positive reactions appeared slightly increased on the final retest. In a number of children the infiltration was decreased or markedly lessened, apparently regardless of the effect on the size of the test reaction. It is interesting to note that one child (D. K.), in whom the Dick test though not reduced in size was definitely less infiltrated than the original, developed a mild but typical case of scarlet fever two months after the retest.

In the group in which Dick retests were given twice, it is worth noting that one child who gave a negative reaction in the first retest gave a slightly positive reaction from five to seven months later; in four others, the second test showed a somewhat larger reaction than the first. On the other hand, one child with a slightly positive reaction gave a negative reaction from five to seven months later; in another, the reaction became reduced in size.

These results, so far as conclusions may be drawn from so small a series, do not seem to indicate a sufficient degree of immunization with the ricinoleated toxin.

In this connection it may be mentioned that in two instances an attempt was made to immunize older children who had been exposed to scarlet fever by giving them two injections of scarlet fever antigen manufactured by Eli Lilly and Company after they had given strongly positive reactions to the Dick test. This antigen is made with sodium ricinoleate according to Larson's method and consists of a scarlet fever streptococcus vaccine containing 3,000 skin test doses of toxin. In neither instance did the Dick reaction become lessened when a retest was made a month later.

Mention should be made that Kozlowski [13] concluded that the supposed detoxifying effect of sodium ricinoleate may not depend on its physicochemical reactions with the bacterial products, but that it is probably due to the destruction of animal tissues in the area of injection. He

13. Kozlowski, A.: The Effect of Ricinoleated Vaccine of the Hemolytic Streptococcus (Scarlet Fever) on Animals, J. Immunol. **15**:115, 1928.

does not recommend soap vaccine for use in clinical practice. Larson,[14] in reply, stated that soap prepared from fatty acids which have been purified with barium invariably causes abscesses, and he attributed the tissue destruction noted by Kozlowski to the presence of barium in the latter's preparation. Larson has long since discontinued that method of purification, but his preparation, which was used in the cases reported in this paper, has apparently failed to induce immunity in a sufficient number of persons in the series.

TESTS WITH DIPHTHERIA TOXOID

Considerably better results with immunization against diphtheria were obtained with toxoid furnished by Miss M. B. Kirkbride of the Division of Laboratories and Research, New York State Department of Health. The toxoid was prepared somewhat after the method of Ramon,

TABLE 2.—*Results of Schick Tests Before and After Administration of Diphtheria Toxoid* *

Name	Age, Years	Sex	Schick Test 3/18/27	Schick Retest 12/17/27
W. M.	12	M	++	Negative
J. M.	5	M	++	+
F. R.	6	M	+	Negative
L. G.	6	F	++	Negative
V. G.	3	F	++	Negative
F. E.†	12	M	++	Negative
H. C.‡	1	F	++	Negative

* Reactions under 1 cm. in one diameter have been noted as +; reactions greater than 1 cm. in one diameter have been noted as ++.
† Fever and local reaction 10 × 9 cm. after first dose.
‡ Slight local reaction after first dose.

but without complete detoxication. Only two doses, each 0.5 cc., were given two weeks apart. This group was composed of seven children, from 1 to 12 years of age (table 2). After the first injection, a child aged 12, gave a local reaction 10 by 9 cm. in diameter, and a child aged 1 year, gave a reaction 2 by 2 cm. in diameter. Reactions did not occur after the second injection. The retest was made nine months later. In the original test, six children gave moderately positive and one a slightly positive reaction. In the retest, six gave negative reactions, and one who at first gave a moderately positive reaction now gave a slightly positive reaction. This compares extremely well with the immunization results after administration of toxin-antitoxin. Of a group of about 1,000 children in Syracuse, the majority of school age, who were given three doses, only 69 per cent gave negative reactions to the Schick test a year or more later. The toxoid has the advantage of containing no serum and requiring but two doses of 0.5 cc. each.

14. Larson, W. P.: Ricinoleated Streptococcic Vaccines, J. Immunol. **15**:299, 1928.

If the result obtained in this small series is an indication of what might be expected in larger groups, the question might be raised as to the advisability of replacing the toxin-antitoxin mixture with toxoid. In a personal communication, Miss Kirkbride expressed the opinion that although the fact that toxoid does not contain horse serum is a definite advantage, this is not sufficient to warrant a change at the present time. Toxoid induces in general more severe local reactions, especially in older children. The immunity response is apparently neither more rapid nor more generally effective. There is some question about the permanence of the immunity; at least, there seems to be some evidence that two doses of toxoid give less permanent immunity than three doses of toxin-antitoxin. The preparation of toxoid is more difficult and expensive, and the longer interval between injections might prove confusing and less convenient. Finally, the probability of sensitization to serum by means of toxin-antitoxin is not definitely established; therefore, the advantage of toxoid would appear to be largely theoretical.

SUMMARY

1. Of a group of seventeen children who were given combined scarlet fever and diphtheria ricinoleated vaccine and tested with the Schick and Dick tests before and after the injections, only one gave a negative reaction to both tests. In six others, the Schick reaction alone was negative, and in one, the Dick reaction alone was negative.

2. One child developed scarlet fever about a year after the three injections; his reaction to the Dick test had become fainter and less infiltrated but not smaller in area; his reaction to the Schick test had become negative.

3. When seven children who had given positive reactions to the Schick tests were given toxoid, six were found to have negative reactions after nine months.

4. There would seem to be little advantage, however, in toxoid over the 0.1 L + toxin-antitoxin mixture, since the latter is reported to have little or no effect on subsequent injections of serum, and the evidence to the contrary is not supported by controls or by sensitivity tests prior to the administration of toxin-antitoxin.

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ANIMAL SERUM IN MEASLES

RESULTS WITH FERRY AND WITH DEGKWITZ SERUM *

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Renewed interest in the problems connected with measles has been steadily increasing in the past ten years. It may be said to have begun with the inconspicuous publication by Nicolle and Conseil [1] in 1918. In the past five or six years particularly, there have appeared numerous reports on the results with convalescent serum and many studies dealing with researches on the etiology and on the production of prophylactic and therapeutic serums. At the same time, epidemiologists have been pointing out that the general measures used in the effort to control epidemic diseases have been of little avail in measles, and they have emphasized the need of administrative methods based on the exact knowledge of the natural history of the disease.[2]

During the measles epidemic in Syracuse extending from 1926 to 1928, more than 8,000 cases were reported. In anticipation of this outbreak a plan was worked out at the end of 1925,[3] which is substantially like that of Copeman published in 1927.[4] While the use of convalescent serum in young children comprised the main effort,[5] opportunities were sought for testing the efficiency of the new experimental serums.

REVIEW OF THE LITERATURE

Smallpox and diphtheria are the best examples of control by vaccination and active immunization. The resemblance of measles to

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* From the Department of Pediatrics, College of Medicine, Syracuse University, and from the Syracuse Health Department and Health Demonstration.

1. Nicolle, C., and Conseil, E.: Pouvoir préventif du sérum d'un malade convalescent de rougeole, Bull. et mém. Soc. méd. d. hôp. de Paris **42**:337 (April 12) 1918.

2. Brownlee, John: Public Health Administration in Epidemics of Measles, Brit. M. J. **1**:534 (April 17) 1920. Godfrey, E. S.: The Administrative Control of Measles, Am. J. Pub. Health **16**:571 (June) 1926. Copeman, W. S. C.: On Some Recently Developed Methods for Measles Prophylaxis, J. Hyg. **24**:27, 1925; The Prophylaxis of Measles with a Suggested Scheme for Dealing with Epidemics, Proc. Roy Soc. Med. **20**:79 (Aug.) 1927.

3. Ruhland, G. C., and Silverman, A. C.: What Can We Do About Measles? Am. J. Pub. Health **18**:131 (Feb.) 1928.

4. Copeman (footnote 2, fourth reference).

5. Silverman, A. C.: Serum Prophylaxis in a Measles Epidemic, J. A. M. A. **91**:1786 (Dec. 8) 1928.

smallpox in many respects led to the attempt by Home,[6] in 1758, to produce a mild attack by a method similar to variolation. He rubbed blood from a patient with measles into scratches made in the skin of susceptible children. In 1850, Mayr [7] produced the disease in a modified form by means of nasal mucus taken from an early case of measles. In recent years, in this country this method has been elaborated by Herrman [8] who applied it to young infants during their natal immunity. This method, however, has not become popular, and the objections to it are voiced by McNeal.[9] Richardson and Connor [10] endeavored to improve this method by the concomitant injection of convalescent serum, making it really a method of serovaccination.

Since Hektoen [11] established that the etiologic agent of measles is present in the blood at the beginning of the rash, Hiraishi and Okamoto [12] endeavored to produce immunity by using tiny quantities of diluted blood taken from a patient during the catarrhal stage of the disease. Debré and his co-workers,[13] in a small series, recently tried two injections of diluted virulent blood, giving 1/800 cc. as the first dose, and 1/400 cc. as the second dose, after an interval of three weeks. While this appears promising and may be found to offer a means for active immunization in the future, it is at present only in the early stage of experimentation.

In the meantime, other workers have attempted to find the etiologic agent first, and then to work out a means for passive immunization and therapy. The work of Caronia, in Italy, is reviewed by McCartney [14] who concluded that the former's claims are unjustified. Redlich [15] came to the same conclusion.

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6. Home, Francis: Medical Facts and Experiments, London and Edinburgh, A. Millar, 1759.

7. Mayr, Franz: Quoted by Hebra: Diseases of the Skin, translated by C. H. Fagge, London, The New Sydenham Society, 1866, vol. 1, p. 182.

8. Herrmann, Charles: Immunization Against Measles, Arch. Pediat. **32**:503, 1915; Immunization Against Measles, ibid. **39**:607 (Sept.) 1922; Recent Progress in the Communicable Diseases of Childhood: I. Measles, New York State J. Med. **23**:93 (March) 1923.

9. McNeal, M. D.: The Serum Prophylaxis of Measles, J. A. M. A. **78**:340 (Feb. 4) 1922.

10. Richardson, D. L., and Connor, Hilary: Immunization against Measles, J. A. M. A. **72**:1046 (April 12) 1919.

11. Hektoen, Ludvig: Experimental Measles, J. Infect. Dis. **2**:238, 1905; Experimental Measles, J. A. M. A. **72**:177 (Jan. 18) 1919.

12. Hiraishi, S., and Okamoto, K.: On Prophylactic Inoculation against Measles, Japan M. World **1**:10 (Oct.) 1921.

13. Debré, R., and Joannon, P.: La Rongeole: Épidémiologie, Immunologie, Prophylaxie, Paris, Masson et Cie, 1926.

14. McCartney, J. E. A Review of Recent Work on Measles, Lancet **1**:93 (Jan. 8) 1927.

15. Redlich, F.: Masernfragen, Monatschr. f. Kinderh. **34**:278, 1926.

In this country, in 1917, Tunnicliff [16] isolated a green diplococcus, and more recently she developed a skin test [17] for determining susceptibility and a serum for use in prevention and modification,[18] for which satisfactory results are reported.[19] An opportunity was not afforded to make use of this material during the epidemic at Syracuse.

Ferry and Fisher [20] reported on the use of an antitoxin produced with a green streptococcus differing somewhat from the Tunnicliff organism. McCartney [14] analyzed their claims and found them unjustified on the evidence presented. Long and Cornwell [21] failed to find a toxin-producing streptococcus in measles. Park [22] presented arguments against the acceptance of an etiologic relationship between measles and either the Tunnicliff or the Ferry organism.

RESULTS WITH THE FERRY ANTITOXIN

Through the courtesy of Dr. Park, some of the Ferry goat serum was made available in the summer of 1926. In two cottages of an orphans' institution in which children over 4 years of age were exposed to measles between July 11 and 16, there were four children in one and seven in the other who supposedly had not had measles. On July 20,

16. Tunnicliff, Ruth: The Cultivation of a Micrococcus from Blood in Pre-Eruptive and Eruptive Stages of Measles, J. A. M. A. **68**:1028 (April 7) 1917.

17. Tunnicliff, Ruth: Further Studies on a Diplococcus in Measles, J. Infect. Dis. **37**:193 (Sept.) 1925. Tunnicliff, Ruth, and Taylor, R. E.: Skin Tests in Measles, J. A. M. A. **87**:846 (Sept. 11) 1926.

18. Tunnicliff, Ruth, and Hoyne, A. L.: Further Studies on Diplococcus from Measles: Prevention of Measles by Immune Goat Serum, J. Infect. Dis. **38**:48 (Jan.) 1926; Prevention of Measles by Immune Goat Serum, J. A. M. A. **87**:2139 (Dec. 25) 1926.

19. Hoyne, A. L., and Gasul, B. M.: Measles Prophylaxis: Report on the Use of Immune Goat Serum, J. A. M. A. **87**:1185 (Oct. 9) 1926. Halpern, L. J.: Prevention and Modification of Measles by Measles Anti-Diplococcus Goat Serum, J. A. M. A. **90**:1109 (April 7) 1928. Hoyne, A. L., and Peacock, S.: Prevention and Modification of Measles with Antimeasles Diplococcus Goat Serum, Am. J. Dis. Child. **35**:1021 (June) 1928.

20. Ferry, N. S., and Fisher, L. W.: Measles Toxin: Its Preparation and Application as a Skin Test, as an Immunizing Agent and for the Production of an Antitoxin, J. A. M. A. **86**:932 (March 27) 1926. Ferry, N. S.: Studies on Etiology of Measles, Am. J. Pub. Health **17**:565 (June) 1927.

21. Long, P. H., and Cornwell, A. M.: Observations on the Etiology of Measles, J. Infect. Dis. **40**:408 (March) 1927.

22. Park, W. H.: Studies of the Etiology and Prevention of Measles, City of New York, Department of Health Weekly Bulletin, (Jan. 8) 1927, vol. 16. Park, W. H.; Williams, A. W., and Wilson, M.: Relation of Tunnicliff and Ferry Diplococci to Measles, Am. J. Pub. Health **17**:460 (May) 1927. Park, W. H.: Abstract of Discussion of Cary, W. E., and Day, L. A.: The Etiology of Measles, J. A. M. A. **89**:1206 (Oct. 8) 1927.

in one cottage, two children were given 5 cc. of serum each and two were kept as controls, and in the other cottage five were given the serum and two kept as controls. A slight rise in temperature (from 100.5 to 101.5 F. rectally) and localized redness (3 by 6.5 cm.) were observed in two children the following day. On July 24, four days later, one of the children who had been inoculated showed the onset of measles. He became extremely ill, ran a high temperature and had an extremely marked rash. Clinically, the disease did not appear at all modified. None of the other children treated, nor any of the controls, developed measles; three of those who were thought to be immune, however, did develop measles. Whether those who were inoculated were really nonimmunes cannot be said with certainty.

In another orphans' home, six children, presumably nonimmune, were exposed to a patient with measles who had developed the rash there on July 28. The patient was removed that day and immediately 5 cc. of serum was given to the two youngest children, aged 3 and 4; the other four being kept as controls. Later the same day the child, aged 3 years, began to show fever and catarrhal symptoms. The fever and rash were slight. No other cases developed.

Obviously, no definite conclusions can be drawn from this experiment. In one case, when the serum was injected four days previous to the onset, no modification occurred. In the other case the serum was given only a few hours before the onset, but the attack was mild. In both, the serum may not have exerted any influence. The preventive value cannot be ascertained, because of the lack of definite knowledge as to the actual exposure and the correct history of a previous attack.

This is a difficulty often encountered in an experiment in children's institutions, so that the results may lead to fallacious conclusions, as pointed out by Redlich.[15] Sometimes, apparent exposure of susceptible persons is not followed by disease even when preventive methods are not practiced. Account should be taken also of the distance of each child from the source of infection. This may be important, because I have frequently observed that infection does not follow in the absence of close contact. This is particularly likely to happen in connection with patients with measles who do not exhibit coughing and sneezing until shortly before the appearance of the exanthem.

Rash Modification by Serum Given Intracutaneously.—Based on the experience with the rash extinction test [23] in scarlet fever, some experi-

23. Toomey, J. A., and Nourse, J. D.: Extinction Tests in Scarlet Fever, Am. J. Dis. Child. **27**:95 (Feb.) 1924. Birkhaug, K. E.: Studies in Scarlet Fever: Studies Concerning the Blanching Phenomenon in Scarlet Fever, J. Clin. Investigation **1**:275 (Feb.) 1925. Toomey, J. A.; Braun, S., and Halperin, I.: Studies in Scarlet Fever, Am. J. Dis. Child. **33**:197 (Feb.) 1927.

ments were made with the goat serum on persons with the measles rash. One cubic centimeter was injected intracutaneously into patients with well marked, early and late eruptions. In eight different tests the result was negative, except that at forty-eight hours, when the rash was fading, two looked suggestive of blanching. The failure to blanch the rash is probably not at all significant as convalescent measles serum likewise fails to blanch the rash. This failure may be analogous to the failure of the blanching test in scarlet fever when the rash is of the papulated variety.

On the other hand, if measles convalescent serum is injected intracutaneously shortly before the appearance of the rash, a local inhibition of the eruption occurs.[13] The phenomenon which Debré described and which is called by Copeman [4] "the phenomenon of Debré" has been confirmed by Keller and Moro.[24] Incidentally, this disproves Pirquet's theory [25] of the mechanism of the measles exanthem.[24]

Four tests with 1 cc. of serum intracutaneously twenty-four hours before the appearance of the rash failed to show this inhibition. In two of these there was an area of erythema about 5 cm. in diameter at the point of injection, but even through the erythema the measles rash could be seen.

Further Attempts at Passive Immunization.—In the spring of 1927, a small supply of the streptococcus antimeasles serum was sent to me through the courtesy of Dr. Ferry and Parke, Davis and Company. This was horse serum of a somewhat lower titer, so that 10 cc. was advised as an immunizing dose. One pediatrician gave a dose to a child, aged 2 years, three days after exposure. Six days later, the child developed a fairly severe case of measles. Another child, aged 5, was given the 10 cc. dose five days after exposure. Fifteen days later he developed a severe case of measles. No report was made as to the serum reactions. One physician gave the serum to three children aged from 9 to 30 months, supposedly three days after exposure. All developed moderate serum reactions, and all developed measles four days later. Even assuming that the serum was given late, modification or attenuation of the disease was not evident.

From the foregoing results, it is obvious that my experience with the Ferry serum does not show any definite evidence of its value.

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24. Keller, W., and Moro, E.: Immunobiologische Masernstudien, Klin. Wchnschr. **4**:1719, 1925.

25. Pirquet, C.: Das Bild der Masern suf der aussern Haut, Ztschr. f. Kinderh. **6**:1, 1913. Mayerhofer, E.: Die Pirquetsche Maserntheorie im Rahmen einer allgemeingiltigen biologischen Regel der fraktionierten Absättigung, Ztschr. f. Kinderh. **38**:244, 1924.

RESULTS WITH DEGKWITZ SERUM

Degkwitz [26] claimed to have grown the virus of measles as obtained from the blood or nasal mucus in early cases, and with it to have produced a sheep serum which can be used in treatment. Besides his favorable reports, there were those of Wiese [27] and Spreitzer.[28] In children's institutions, they gave it to all those supposed to be susceptible on from the seventh to the ninth day after the appearance of the first case of measles. On the other hand, several other workers found that the serum did not exert any influence on the course of measles, and some obtained severe serum reactions.[29] Redlich [15] also found it of no value whether given early or toward the end of the incubation period. Zoepfel [30] tried the Degkwitz serum in one group and adult immune serum in another group in the same institution and concluded that the sheep serum is a failure.

My experience with this serum came in the spring of 1927, after a talk with Professor Degkwitz. The material was sent by the H. K. Mulford Company, through the courtesy of Dr. F. M. Huntoon, and consisted of syringes containing 10 cc. of antimeasles serum Degkwitz. The instructions that accompanied were strictly followed. It was felt that if something that would mitigate the disease could be used in the invasion period a valuable factor in the treatment of measles would be available.

An outbreak among some institutional children, aged 4 years or older, who ordinarily would not be given convalescent serum, afforded an opportunity to test the sheep serum. In two different cottages in

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26. Degwitz, R.: The Etiology of Measles, J. Infect. Dis. **41**:304 (Oct.) 1927; Spezifisches Masernschutzserum vom Tier, München med. Wchnschr. **73**:181 and 248 (Jan. 29 and Feb. 5) 1926; Weitere Erfahrungen mit Masernserum vom Tier, Klin. Wchnschr. **5**:1361, 1926.

27. Wiese, Otto: Erfahrungen mit dem neuen Masern-Tierserum nach Degkwitz, München med. Wchnschr. **73**:184 (Jan. 29) 1926.

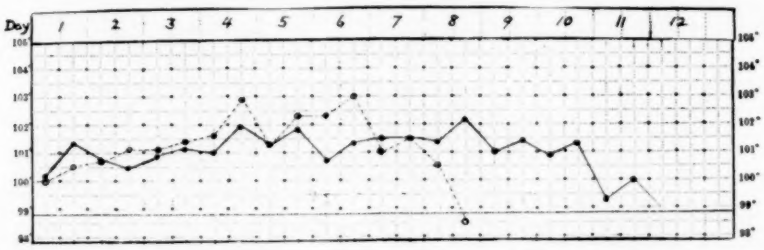
28. Spreitzer, O. H.: Erfahrungen mit dem tierischen Degkwitzschen Masernserum, München med. Wchnschr. **74**:1089 (July 4) 1927.

29. Kaupe, W.: Degkwitz' Measles Serum, Med. Klin. **22**:213 (Feb.) 1926; abstr., J. A. M. A. **86**:1173 (April 10) 1926. Kochmann, R.: Degkwitz' Measles Serum, Deutsche med. Wchnschr. **52**:565 (April) 1926; abstr., J. A. M. A. **86**:1875 (June 12) 1926. Noeggerath, C., et al.: Degkwitz' Measles Serum, Klin. Wchnschr. **5**:1168 (June) 1926; abstr., J. A. M. A. **87**:887 (Sept. 11) 1926. Seligmann, E., et al.; Prevention of Measles, Deutsche med. Wchnschr. **52**:1220 (July) 1926; abstr., J. A. M. A. **87**:1164 (Oct. 2) 1926. Erichson, K.: Degkwitz' Measles Serum, Med. Klin. **22**:1332 (Aug.) 1926; abstr., J. A. M. A. **87**:1781 (Nov. 20) 1926. Baron, C.: Degkwitz' Measles Serum, Med. Klin. **23**:48 (Jan.) 1927; abstr., J. A. M. A. **88**:1527 (May 7) 1927.

30. Zoepfel, H.: Vergleichende Erfahrungen mit tierischen Masenschutzserum und mit Blut durschmaserter Erwachsener, München med. Wchnschr. **74**:150 (Jan. 28) 1927.

which measles occurred, three children were given the serum and four kept as controls in each, and in a third cottage, seven were given the serum and three kept as controls. The probable time of exposure was known, and the taking of temperatures twice daily made it possible to ascertain the first rise of temperature to 100 F. or more rectally, indicating the advent of the invasion. In practically all cases, this occurred on about the ninth day, and five days after the appearance of the rash in the source of infection. At this time the serum was given to the children, in accordance with Degkwitz's instructions. One child received only half a dose. Only one really severe serum reaction occurred in this group and that within three hours of the injection.

The first difficulty that evidenced itself was that the first rise in temperature to 100 F. or more did not always indicate the beginning of the invasion. Thus, one child with the first rise in temperature on the ninth day after exposure did not develop measles; he may have been immune. Three other children became normal after the first rise



Average morning and afternoon temperatures of the febrile period in ten uncomplicated cases of measles in which the patients were given Degkwitz serum, and in ten uncomplicated cases in which the patients were treated without serum. The solid lines and heavy dots represent the children treated with Degkwitz serum; the broken lines and circles represent the children not treated with Degkwitz serum.

in temperature and further symptoms of invasion did not appear until three, four and six days, respectively, after the injection of serum. In other words, in these three, the serum was apparently not given on what purported to be the first day of the invasion period, but in reality on about the sixth, fifth and third days, respectively, of the incubation period. Thus, only nine of the twelve patients receiving serum, who subsequently developed measles, received it on about the ninth day, and the other three in the earlier stage of the incubation, as indicated previously.

The type of disease which these children developed did not seem clinically modified. Severe and mild cases occurred in the children treated as well as in those untreated. When the duration of the febrile

period and the height of the fever were compared in the two groups, the children treated fared slightly worse than those untreated (chart 1).

There seemed to be little difference in those who received the serum at the end of the incubation period as compared with the three who received it earlier in the incubation period. Only one child developed bronchopneumonia and he was a child treated with serum; his temperature record was not included in computing the duration and height of fever in the children treated. Despite the fact that this is a small series, it seems fair to conclude that the serum did not appear to modify the disease favorably.

Another instance of a severe serum reaction and the development of bronchopneumonia as a complication of measles was seen in a private case. The child, aged 6, was exposed to measles at school and had her first rise of temperature on May 22. That evening 10 cc. of Degkwitz serum was given. Within twenty-four hours the temperature rose to 103 F., she vomited repeatedly and a severe cough began. The next day, May 24, the temperature rose to 105 F., and there was a generalized diffuse flush on the face and trunk. Conjunctivitis and Koplik spots were present at this time. A morbilliform rash began to show on the neck and forehead in the morning but vanished that evening and was followed by a generalized erythema the next day, May 25, which persisted until May 29. The fever stayed at 105 and 106 F., and signs of bronchopneumonia appeared.

In a physician's family, one child, aged 7, and one, aged 3, were definitely exposed to measles on May 14. The younger child was given 4.5 cc. of convalescent measles serum on May 21, seven days after the last exposure. Her first rise of temperature occurred on May 26. The next day there was coryza, and on the following day a beginning rash. The highest rectal temperature, 102 F., was present on May 28 and 29. The child hardly appeared ill and it was almost impossible to keep her in bed. The older child was to be given Degkwitz serum on the first appearance of fever. On May 21, seven days after exposure, she was therefore given 0.2 cc. of the serum as a desensitizing dose. Within half an hour there was a wheal, 2 cm. in diameter, surrounded by a zone of erythema, 6 cm. in diameter. The first rise of temperature occurred on May 24, and 10 cc. of Degkwitz serum was given intramuscularly. On May 27, the rash appeared; at this time the child also showed a localized serum reaction. The coryza was marked, the temperature was moderately high and the rash profuse on May 29. At the site at which the desensitizing dose was given, a blanched area 2 by 2 cm. was present. In general, the child's father and I felt that the disease had not been mitigated by the sheep serum, whereas in the case of the younger child who had been given convalescent serum there was no question of modification.

CONCLUSION

It seems, therefore, that the Degkwitz serum in the fourteen cases of measles did not show any results of value; at least two children developed severe serum reactions, so severe perhaps as to influence the condition unfavorably, and in two, the complication of bronchopneumonia occurred.

THE ULTRAVIOLET COMPONENT OF THE SUNLIGHT OF PORTLAND, ORE.

MEASURED BY THE ACETONE-METHYLENE BLUE METHOD *

IRA A. MANVILLE, M.D.

PORTLAND, ORE.

In 1919, Huldschinsky [1] pointed out the value of ultraviolet rays in the healing of rickets. Somewhat later, Hess and Unger [2] and others reported that sunlight possessed the same beneficial action on rickets that ultraviolet light had. According to McCollum,[3] cod liver oil has been used for at least one hundred years for conditions that were probably of a rachitic nature. The ability of medical agencies as well as of hygienic ones to affect favorably the outcome of a rachitic process moved Park, Powers and Guy [4] to remark that "the similarity between the action of cod liver oil and that of radiant energy in rickets is so close that a connection must exist between them."

In 1924, Hess [5] and Steenbock and Nelson,[6] working indepently, were able to demonstrate that various foods known to be inadequate in the cure of rickets could be made therapeutically potent by exposing them to the action of ultraviolet radiations. Thus a means that might be difficult to obtain directly was made available in an indirect manner and a partial explanation was provided for the connection existing between cod liver oil and radiant energy aforementioned. Later, these same investigators [7] found that the substance which was thus transformed from an impotent to a potent antirachitic agent seemed to be

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* From the Department of Physiology, University of Oregon School of Medicine.

1. Huldschinsky, K.: Deutsche med. Wchnschr. **45**:712, 1919.

2. Hess, A. F., and Unger, L. J.: Cure of Infantile Rickets by Sunlight, J. A. M. A. **77**:39 (July 2) 1921.

3. McCollum, E. V., and Simmonds, Nina: The Newer Knowledge of Nutrition, Baltimore, Johns Hopkins Press, 1925, p. 365.

4. Park, E. A.; Powers, G. F., and Guy, R. A.: Regulatory Influence of Cod Liver Oil on Calcium and Phosphorus Metabolism, Am. J. Dis. Child. **26**:103 (Aug.) 1923.

5. Hess, A. F.: Experiments on the Action of Light in Relation to Rickets, Am. J. Dis. Child. **28**:517 (Oct.) 1924.

6. Steenbock, Harry, and Nelson, M. T.: Science **60**:224, 1924; J. Biol. Chem. **62**:209 (Nov.) 1924.

7. Hess, A. F., and Weinstock, Mildred: J. Biol. Chem. **63**:25, 1925. Steenbock, Harry; Black, A.; Nelson, M. T., and Hoppert, C. A.: J. Biol. Chem. **63**:25, 1925.

cholesterol. Still later, it was shown by Windaus and Hess [8] and by Rosenheim and Webster [9] that the specific substance undergoing activation was ergosterol and not cholesterol. A full explanation for the aforementioned relationship was provided by Hess and Weinstock [10] when they showed that irradiated human skin would protect rats from the development of rickets. It was assumed that the ergosterol located in the cutaneous tissues became activated by exposing the skin to the influence of ultraviolet radiations and produced a general systemic response because of its ability to circulate in the blood stream. It makes little difference whether this activated material is absorbed from the cutaneous tissues or from the digestive tract, unless, perchance, the ability of the digestive organs to digest fats is impaired. In the latter event, it is obvious that cutaneous irradiation or the parenteral introduction of activated materials would be of more certain value. In some preliminary work it would appear that pups made acholic by biliary fistulas develop rickets notwithstanding the fact that they receive cod liver oil.[11]

The aforementioned researches serve to point out the fact that the ultraviolet rays of sunshine are capable not only of effecting a cure in rickets but also are able to produce such changes in foods that when they are ingested, the rachitic process will be either prevented or corrected. It appears that in the prophylaxis or cure of rickets, recourse must be had either directly or indirectly to the action of sunlight or its substitutes. The only substitute for this activity is the use of certain lamps whose light is rich in those wave lengths found to have specific powers in this respect. Obviously there can be no wholesale application of these artificial substitutes, for the time still lies in the future when artificial sources of ultraviolet radiations will be employed extensively in the raising of foodstuffs; nor, in the light of present knowledge, would this plan be unequivocably advisable. Even the general clinical use of ultraviolet light of nonsolar origin is beset with considerable difficulty, for not only are there technicalities not satisfactorily settled, but to many the economic aspect as well will act as a barrier.

For many years, sunlight has been used as a source of ultraviolet light, but with considerable difficulty since the richness of sunshine in those wave lengths falling within the range of ultraviolet rays varies because of several factors, most of which are beyond control. Hill,[12] for

8. Windaus, A., and Hess, A. F.: Gesellsch. d. Wissensch. z. Gottingen, Math.- Phys. Klasse, 1925, p. 195.

9. Rosenheim, O., and Webster, T. A.: J. Soc. Chem. Indust. **45**:932, 1926.

10. Hess, A. F., and Weinstock, Mildred: Proc. Soc. Exper. Biol. & Med. **22**:319, 1925.

11. Unpublished data from the laboratory of the Department of Physiology.

12. Hill, L.: Proc. Roy. Soc. London **102**:119, 1927-1928.

example, presents the situation clearly when he lists the following factors as causes for variation in the amount of the ultraviolet component sunlight: (*a*) the source, whether skyshine or sunshine; (*b*) the time of day; (*c*) the time of year; (*d*) the pollution of the air; (*e*) the geographic location, and (*f*) altitude.

By recording simultaneous readings of ultraviolet rays from both skyshine and sunshine, Hill [13] found "that the total ultraviolet radiation from the sky is far more than from the direct sun." Dorno [14] determined that the ultraviolet rays from skyshine were 15 per cent greater in amount than those from sunshine or, in other words, that the ultraviolet radiation of the sun even when the sun is at its zenith is only about 90 per cent of that of skyshine. Tisdall and Brown [15] showed that for Toronto the ultraviolet radiation of the skyshine during the latter part of April and the first part of May, 1927, averaged 30 per cent more than that contained in sunshine, and that the antirachitic effect of skyshine alone was approximately from one-half to two-thirds as great as that produced by sunshine and skyshine acting together. From the foregoing observations, it is obvious that to get maximal results from heliotherapy one must be assured that direct solar radiations, as well as those that are indirect or diffuse, are being received and that it is not necessary to discard all solarization because direct sunshine is not available.

The diurnal variation in the amount of ultraviolet radiation in the sunlight is due to the differences in the height of the sun as it takes its daily course across the sky. Dorno [14] has shown that sunlight is weak in ultraviolet rays in the early morning and evening and that the greatest intensity occurs between the hours of 10 a. m. and 1 p. m. This is due to the fact that the atmospheric layer is thicker and the absorption of ultraviolet rays greater with the sun low in the heavens than when it is high. As the sun climbs from its position at 5 a. m. to its place at noon, radiations that reach the earth are from 5 to 17 millimicrons shorter.

The seasonal differences in the amount of ultraviolet light contained in the sunshine varies in the same manner and from the same causes as the diurnal variation but are greater in degree. In the winter, diurnal variation in wave lengths fall within 5 millimicrons, in the spring and fall within 12 millimicrons and in the summer within 17 millimicrons.[16] Dorno [14] found that the ultraviolet content of the sun

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13. Hill, L.: Nature, London **115**:642, 1925.

14. Dorno, C.: Klimatologie in Dienste der Medizin, Brunswick, Vieweg & Son, 1920.

15. Tisdall, F. F., and Brown, Alan: Antirachitic Effect of Skyshine, Am. J. Dis. Child **34**:737 (Nov.) 1927.

16. Hess, A. F.: The Ultraviolet Rays of the Sun, J. A. M. A. **84**:1033 (April 4) 1925.

at noon in Davos, Switzerland, was 10 per cent as great in January as in July. Sheard,[17] quoting from others, stated that July furnishes the maximal amount of ultraviolet light in the sunlight and that in December and January this value reaches its lowest level, or less than 5 per cent of the July total. Thus it will be seen that in the winter when the zenith distance of the sun is persistently greater than in the summer, the loss in ultraviolet radiation is both quantitative and qualitative. Hess [16] has shown (*a*) that the antirachitic value of sunlight is not dependent on the total or average number of hours of actual sunshine either for the year or for the season; (*b*) that it has no relationship to an equable distribution of sunlight throughout the year and (*c*) that it is due to the quality of sunlight rather than its quantity. He found that rats with experimentally produced rickets obtained little protection when exposed to diffuse daylight for four hours a day during the month of December, and that only incomplete protection was obtained during May. He further stated that the sunlight in New York cannot be relied on for affecting a cure of rickets in the winter although it can be depended on during the summer. Bundesen, Lemon and Coade, working in Chicago, found that in December, 1926, the wave lengths of the ultraviolet end of the spectrum were between 3,030 and 3,150 angstrom units and that in May, 1927, they were between 3,000 and 2,990.

Various investigators who have measured the amount of ultraviolet light in sunshine under different kinds of atmospheric pollution have found remarkable losses due to such destructive factors as smoke, fog and dust. Hill [12] found that the sunlight was much richer in ultraviolet light in places remote from towns, such as Peppard Common and the top of Hampstead, than in industrial areas such as Kingsway and Hull (chart 1). He said [13] that "smoke pollution robs us of half or more of the ultraviolet rays." The Medical Research Council of England reported [18] that, on the average, two thirds of the ultraviolet light in the sunshine of London was cut out by smoke and dust. Measurements made by the U. S. Public Health Service of the average loss of daylight due to smoke in New York, at the lower end of Manhattan Island,[19] showed that in January, 1927, there was a loss of 42 per cent at 8 a. m. and of 18 per cent at noon. They reported that, as the year progressed, the loss became less so that in June a loss of only 6 per cent was recorded at noon. It was stated also that while these losses occurred on bright, sunny days, on foggy days the drop was

17. Sheard, Charles: Ultraviolet Radiation and Its Transmission by Various Substances, J. A. M. A. **88**:1315 (April 23) 1927.

18. Medical Research Council, Annual Report: Lancet **1**:508, 1927.

19. Loss of Light Through Smoke: General Medical News, J. A. M. A. **89**: 1976 (Dec. 3) 1927.

still greater. Bundesen, Lemon and Coade,[20] in measuring the shortening of the spectrum due to smoke, found a difference of 60 angstrom units. They stated that "the reduction of the spectrum limits by smoke, expressed in intensity, is much greater, however, than the change of 60 angstrom units would imply."

The amount of ultraviolet radiation varies also with geographic location. Hill [12] gave the following figures (acetone-methylene blue method) for December, 1926: Hampstead, England, 0.4 units; Davos, Switzerland, 2.3 units, and Assouan, Egypt, 11.4 units. Hess [16] showed that in Ancon and Colon in the Panama Canal Zone and in San Juan, Porto Rico, rickets is practically nonexistent although these cities have little if any more total sunshine than New York. He concluded from these observations that the sunlight in these places was much richer in ultra-

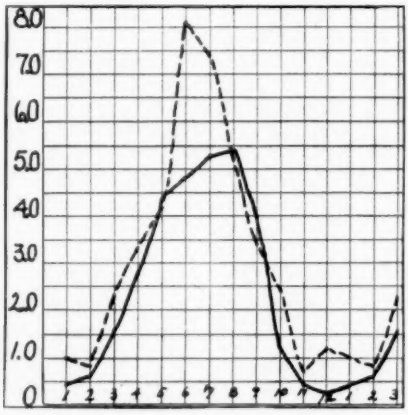

Chart 1.—Comparison between the amount of ultraviolet light in the sunshine of Peppard (broken line), and that of the smoky area of Hampstead (solid line) from January, 1925, to June, 1927. The figures at the left indicate units of ultraviolet light by the acetone-methylene blue scale.

violet rays. Kestner [21] stated that ultraviolet radiation under all meteorologic conditions is stronger in the far North than in central Europe. Elliot [22] stated that the average daily readings of ultraviolet light at Ventnor, Isle of Wight, for November and December, 1926, were 2.35, and that for Edinburgh the readings were nil for the three months between November, 1925, and March, 1926, and that even in March and April the readings only averaged 1.1. Although the manner

20. Bundesen, Herman N.; Lemon, Harvey B., and Coade, E. N.: J. A. M. A. **89**:187 (July 16) 1927.

21. Vitamins of Cod Liver Oil: Berlin Letter, J. A. M. A. **90**:309 (Jan. 8) 1928.

22. Elliot: Lancet **1**:1054, 1928.

of measuring was not given, it is assumed to have been the acetone-methylene blue method.

Dorno [14] showed that the atmospheric absorption of ultraviolet light increased with a decrease in altitude. For example, the loss was found to be four times as great in Kolberg at the level of the Baltic Sea as at Davos in the Alps. Coblentz and others [23] stated that the ultraviolet component of the spectral range lying between 170 and 450 millimicrons was less than 20 per cent in Washington, D. C., which has an elevation of 30 feet, while at Flagstaff, Ariz., with an elevation of 7,000 feet, the value was 30 per cent, an increase of 50 per cent. Hill [13] stated that in the Alps a reading of 41 was obtained in one day, while the highest total reading for one day at Peppard, Oxon, was only 23, by the acetone-methylene blue method.

Consideration of the foregoing facts will at once justify the statement that there is a seasonal as well as a geographic variation in the incidence of rickets. As long ago as 1884, Kassowitz [24] described this aspect of the disease. More recently it was dwelt on by Tisdall and Brown [25] and by Hess.[26] The latter showed that the incidence of rickets bears an inverse relationship to the amount of ultraviolet light in the sunshine and the level of phosphorus in the blood. He spoke of this annual variation in blood phosphorus as the "seasonal tide."

To substantiate the statement that there is a geographic variation in the incidence of rickets, I prepared table 1 from figures given by Williams,[27] Mohr,[28] Hess [16] and Torroella.[29]

While it is undoubtedly true that clinicians vary in their interpretation of a rachitic or nonrachitic condition because of different ideas as to what constitutes adequate criteria for judgment, it need not deter one from a serious consideration of table 1. The differences in incidence show a much greater variation than would probably result from differences in the conception of clinical rickets. All the cities mentioned in the table, except Denver, furnish evidence of the geographic variation in the incidence of rickets. While it is true that Denver, also, can be

23. Coblentz, W. W.; Dorcas, M. J., and Hughes, C. W.: Radiometric Measurements on Carbon Arc and Other Sources Used in Phototherapy, J. A. M. A. **88**:390 (Feb. 5) 1927.

24. Kassowitz, M.: Wien. med. Presse **38**:97, 1897.

25. Tisdall, Frederick F., and Brown, Alan: Seasonal Variation of Antirachitic Effect of Sunshine, Am. J. Dis. Child. **34**:721 (Nov.) 1927.

26. Hess, A. F., and Lundagen, M. A.: A Seasonal Tide of Blood Phosphate in Infants, J. A. M. A. **79**:2210 (Dec. 30) 1922; Seasonal Variation of Rickets, Am. J. Dis. Child. **22**:186 (Aug.) 1921.

27. Williams, C. T.: Infrequency of Severe Rickets in New Orleans and Vicinity, Am. J. Dis. Child. **35**:590 (April) 1928.

28. Mohr, G. J.: Northwest Med. **24**:430, 1925.

29. Torroella: Gac. méd. de México **58**:765 (Dec.) 1927.

included in this category, it would be better still to consider it as exemplifying the variation due to altitude. Because rickets and spasmophila are conditions almost entirely limited to the very young, one should not conceive the idea that the incidence of conditions growing out of a variation in the amount of ultraviolet light or, more indirectly, of vitamin D is limited exclusively to this period of life; in fact, just the contrary is true. On a rachitic status in early life may be superimposed conditions that later result in kyphosis, scoliosis, pes planus, genu valgum, dental caries and, perhaps, other diseases. Thus when a deficiency is once induced and its causes are maintained more or less throughout life, it is necessary to consider those conditions which grow out of a deficiency of ultraviolet light or of vitamin D as being common to all ages.

TABLE 1.—*Geographic Variation in the Incidence of Rickets*

Locality	Rickets, per Cent
Boston	80
New York	50 to 75
Portland, Ore.*	5 to 75
Seattle	30 to 54
New Orleans	26 to 45
Los Angeles	30
Denver	25
San Juan, P.I.	0
Ancon and Colon, Panama Canal Zone	0
Mexico	0
Far North (Eskimos and Scandinavians)	0 (almost unknown)

* In a personal communication to the author, Dr. L. Howard Smith stated that it is his opinion that in Portland and the surrounding community, 75 per cent of the young children show a tendency toward rickets, as evidenced by delayed dentition, retarded closure of the fontanels, potbelly or an outward flare of the ribs, while only from 5 to 10 per cent have the florid type of the disease.

The extremely high incidence of rickets in children and of various osteo-porotic conditions among adults; the variable results obtained by the use of cod liver oil and the uniform results obtained with ultraviolet light irradiations or irradiated foodstuffs, together with the wide divergence in the amount of ultraviolet light in the sunshine and the resultant antirachitic activity of foods grown in this light, have made it extremely advisable to attempt to measure the ultraviolet light value of sunshine in various districts over considerable periods of time. A measure of these wave lengths in the sunlight of this district seemed to me of particular value for two reasons; namely, the incidence of rickets here is high and the annual quota of sunshine quite low as compared with most other districts in the United States. So far as is known, no records of this sort have been kept for any place in the United States or Canada, except those of Best and Ridout.[30] In England, considerable data of this kind has already been accumulated.[12]

30. Best, C. H., and Ridout, J. H.: Am. J. Dis. Child. **34**:719 (Nov.) 1927.

EXPERIMENTAL PROCEDURE

In order to get data that would be comparable to results of a similar nature obtained elsewhere, it was decided to use the acetone-methylene blue method described by Hill.[32] Coblentz,[31] of the Bureau of Standards, Washington, D. C., in discussing the various methods for measuring ultraviolet radiations, stated, "the use of a standard methylene blue and acetone solution as a means of measuring the intensity of the ultraviolet seems feasible." He offered criticism as to (*a*) making up identical solutions at different times and (*b*) the effect of temperature on the reduction. The first difficulty was obviated by preparing enough of the standard solution to last through the period of observation. It was placed in a dark glass bottle which was kept in an icebox. In regard to the second criticism, Tisdall and Brown[25] were of the opinion that the temperature coefficient should be more adequately investigated. Hill,[32] however, determined the temperature coefficient between 1.5 and 35 C. and found it to be from 1.15 to 1.2 for 10 C. He found that a difference of 10 C. above or below 20 C. will make a difference of about half a

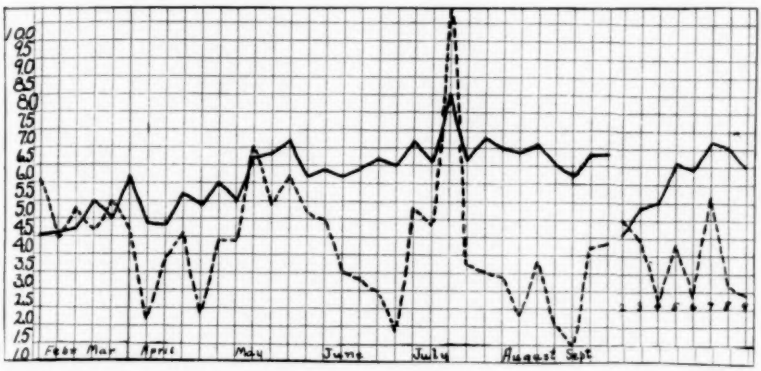

Chart 2.—The weekly average, by the day, of the temperature (solid line) and of the amount of ultraviolet light (broken line) for the period from Feb. 10 to Sept. 28, 1928. The figures in the left hand column, which represent the units of ultraviolet light, can be read as degrees of temperature, by disregarding the decimal point. The curves at the right show the monthly averages by the day.

degree on the scale. As he stated, "such a correction may be required in the tropics or cold climate." In making the records presented in this paper, care was taken to correlate the observations with the temperature curve. Table 2 and chart 2 reveal the fact that there were thirty-three (17 per cent) days having a temperature at noon outside the range of from 50 to 86 (from 10 to 30 C.). If the weekly averages are taken, only five (15 per cent) fall outside the limits and, in the monthly averages, only one (12 per cent). The escape from the limits requiring a correction of five tenths of a point were so few that no attempt was made to institute a correction, especially in view of the fact that the readings were made in favor of the high point on cold days and of the low point on warm days.

The amount of ultraviolet light represented by one unit of the scale may be expressed in two ways: the number of erythema doses, or the power which the light

31. Coblentz, W. W.: Radiology **10**:116, 1928.

TABLE 2.—*The Average Weekly and Monthly Amount of Ultraviolet Light, by the Day, in the Sunlight of Portland, Ore.**

Date	Daily				Weekly				Monthly			
	Sunshine, per Cent	Units Ultraviolet Light	Rainfall	Temperature	Sunshine, per Cent	Units Ultraviolet Light	Rainfall	Temperature	Sunshine, per Cent	Units Ultraviolet Light	Rainfall	Temperature
Feb. 10	100	5.2	0.03	53								
11	92	6.2	0.01	49								
12	70	....	0	39								
13	5	3.0	0.04	46								
14	61	6.0	T†	44								
15	68	7.7	0	42								
16	86	8.5	0	45	69.0	6.1	0.01	45.4				
17	98	6.0	0	54								
18	77	5.0	0	47								
19	44	....	T	41								
20	29	4.0	T	44								
21	0	3.2	0.08	45								
22	0	5.0	0.26	48								
23	2	4.0	T	43	35.7	4.5	0.05	46.0				
24	0	2.0	0.11	40								
25	3	4.0	0.26	47								
26	67	....	0	46								
27	36	5.0	0	49								
28	45	4.0	0	47								
29	7	7.0	0	50					44.5	5.0	0.04	46
March 1	100	10.0	0	53	37.0	5.3	0.05	47.4				
2	100	9.0	0	55								
3	100	2.5	0	59								
4	0	....	0.26	46								
5	15	4.5	0.09	58								
6	11	4.5	0.04	54								
7	18	3.0	0.07	57								
8	1	5.0	0.34	55	35.0	4.7	0.11	55.0				
9	9	4.0	0.43	53								
10	0	1.0	1.16	53								
11	38	....	0.69	52								
12	10	6.0	0	50								
13	1	2.0	0.09	44								
14	63	14.0	0	46								
15	0	6.0	0.18	52	17.0	5.5	0.36	50.0				
16	30	5.0	0	57								
17	97	3.0	0	64								
18	100	....	0	67								
19	82	6.0	0.03	72								
20	0	2.0	0.15	57								
21	5	5.0	0.41	58								
22	29	7.0	0.24	61	49.0	4.7	0.12	62.0				
23	28	3.0	0.39	55								
24	6	....	0.08	46								
25	56	....	0	48								
26	18	3.0	1.08	46								
27	6	2.0	0.29	46								
28	52	2.0	0.05	51								
29	17	1.0	0.06	53	26.0	2.2	0.48	49.0				
30	0	1.0	0.79	52								
31	1	....	0.29	47					32.0	4.46	0.232	53.8
April 1	12	....	0.14	43								
2	11	2.0	0.36	51								
3	52	6.0	0.12	50								
4	3	6.0	0.12	46								
5	50	4.0	0	51	18.4	3.8	0.26	48.6				
6	98	8.0	0	54								
7	100	....	0	59								
8	86	....	0	65								
9	48	5.0	0.04	59								
10	56	4.0	T	54								
11	22	3.0	0.16	55								
12	1	3.0	0.02	54	59.0	4.6	0.03	57.0				
13	30	4.0	0.08	60								
14	39	....	0.05	55								
15	38	....	0.02	61								
16	5	2.0	0.38	57								
17	10	2.0	0.42	50								
18	47	2.0	0.08	50								
19	9	2.0	0.61	42	25.4	2.4	0.23	54.0				

TABLE 2.—*The Average Weekly and Monthly Amount of Ultraviolet Light, by the Day, in the Sunlight of Portland, Ore.*—Continued*

Date	Daily				Weekly				Monthly			
	Sunshine, per Cent	Units Ultraviolet Light	Rainfall	Temperature	Sunshine, per Cent	Units Ultraviolet Light	Rainfall	Temperature	Sunshine, per Cent	Units Ultraviolet Light	Rainfall	Temperature
April 20	35	2.0	0.02	52								
21	0	....	0.35	53								
22	68	....	0	64								
23	3	1.5	0.65	57								
24	44	3.5	0.02	57								
25	72	8.0	0	62								
26	67	7.0	0.02	70	40.0	4.4	0.15	60.0				
27	44	4.0	0.14	56								
28	65	....	0.10	57								
29	27	....	0.04	54								
30	27	3.0	0.53	50					38.0	2.73	0.15	54.9
May 1	41	6.0	0.32	54								
2	35	4.0	0	53								
3	62	5.0	0	63	43.0	4.4	0.16	55.0				
4	72	6.0	0	65								
5	70	....	0	68								
6	85	....	0	64								
7	71	8.0	0	63								
8	100	8.0	0	68								
9	100	7.0	0	66								
10	100	6.0	0	75	85.4	7.0	0	67.0				
11	55	6.0	0	62								
12	87	....	0	64								
13	87	....	0	76								
14	80	5.0	0	79								
15	100	6.0	0	71								
16	57	3.0	0	61								
17	61	7.0	0	62	75.0	5.4	0	68.0				
18	100	7.0	0	70								
19	100	....	0	75								
20	100	....	0	76								
21	47	4.0	T	66								
22	59	7.0	0	64								
23	86	6.0	0	72								
24	99	7.0	0	79	84.4	6.2	0	72.0				
25	54	6.0	0	69								
26	61	....	0	62								
27	48	....	0.03	62								
28	8	5.0	0.14	58								
29	20	5.0	0.25	50								
30	75	7.0	T	60								
31	91	3.0	0	68	51.0	5.2	0.06	61.4	71.0	4.32	0.024	66.0
June 1	21	5.0	0.01	60								
2	59	....	0.01	66								
3	69	....	0	69								
4	58	6.0	0	67								
5	82	7.0	0	65								
6	62	4.0	0.01	62								
7	26	3.0	0	59	54.0	5.0	0.004	64.0				
8	73	4.0	0	64								
9	57	....	0	63								
10	0	....	0.17	58								
11	4	3.0	0.01	64								
12	32	4.0	0	64								
13	8	3.0	0	64								
14	11	4.0	0.06	60	26.4	3.6	0.034	62.4				
15	6	2.0	T	60								
16	18	....	0.08	58								
17	86	....	0	64								
18	100	4.0	0	69								
19	54	3.0	0.07	69								
20	17	4.0	0	66								
21	6	4.0	0	65	41.0	3.4	0.021	64.4				
22	98	3.0	0	69								
23	100	2.0	0	78								
24	27	3.0	0	64								
25	0	2.0	0	65								
26	20	4.0	0	64								
27	2	3.0	T	64								
28	25	3.0	T	64	39.0	3.0	0	67.0				

TABLE 2.—*The Average Weekly and Monthly Amount of Ultraviolet Light, by the Day, in the Sunlight of Portland, Ore.*—Continued*

Date	Daily				Weekly				Monthly			
	Sunshine, per Cent	Units Ultraviolet Light	Rainfall	Temperature	Sunshine, per Cent	Units Ultraviolet Light	Rainfall	Temperature	Sunshine, per Cent	Units Ultraviolet Light	Rainfall	Temperature
June 29	13	3.0	0.02	63								
30	0	2.0	0	63								
July 1	0	1.0	0	62					38.0	2.83	0.014	64.4
2	30	1.0	T	68								
3	22	1.0	0.23	68								
4	31	2.0	0.10	66								
5	16	3.0	0.08	65	16.0	1.86	0.061	65.0				
6	60	2.0	0	67								
7	96	6.0	0	71								
8	54	4.0	0	67								
9	71	6.0	0	68								
10	86	6.0	0	76								
11	100	7.0	0	83								
12	78	6.0	0	70	78.0	5.3	0	72.0				
13	100	6.0	0	69								
14	52	7.0	0	62								
15	81	5.0	0	69								
16	72	4.0	0	66								
17	1	3.0	0	63								
18	32	4.0	T	66								
19	63	5.0	0	67	57.3	4.85	0	66.0				
20	70	7.0	0	70								
21	100	8.0	0	84								
22	100	12.0	0	89								
23	100	12.0	0	87								
24	95	14.0	0	88								
25	79	11.0	0	91								
26	100	12.0	0	87	92.0	10.85	0	85.0				
27	79	6.0	0	75								
28	56	6.0	T	65								
29	40	2.0	T	62								
30	64	3.0	0	67								
31	0	3.0	0.01	62					62.0	5.64	0.013	71.7
Aug. 1	24	4.0	T	66								
2	17	2.0	0	67	40.0	3.71	0.001	66.3				
3	46	3.0	0	71								
4	5	3.0	0	66								
5	68	5.0	0	71								
6	62	4.0	0	75								
7	95	3.0	0	78								
8	64	4.0	0	72								
9	77	3.0	0	77	60.0	3.57	0	73.0				
10	49	4.0	0	76								
11	78	5.0	0	73								
12	83	3.0	0	69								
13	58	4.0	0	70								
14	39	3.0	0	63								
15	78	3.0	0	69								
16	84	2.0	0	73	67.0	3.43	0	70.4				
17	82	3.0	0	71								
18	63	2.0	0	67								
19	46	2.0	0	66								
20	83	2.0	0	70								
21	5	3.0	T	62								
22	69	2.0	0	69								
23	81	2.5	0	75	61.4	2.36	0	68.6				
24	52	2.5	0	76								
25	31	2.5	0	66								
26	0	2.0	0	66								
27	43	4.0	T	68								
28	100	4.0	0	75								
29	100	7.0	0	72								
30	99	4.5	0	74	60.7	3.80	0	71.0				
31	72	2.0	0	74					59.0	3.22	0	70.5
Sept. 1	100	2.0	0	69								
2	61	1.5	0	66								
3	55	1.5	0	65								
4	40	2.0	0	62								
5	0	2.5	T	60								
6	0	3.0	0	62	47.0	2.10	0	65.4				

TABLE 2.—*The Average Weekly and Monthly Amount of Ultraviolet Light, by the Day, in the Sunlight of Portland, Ore.*—Continued*

Date	Daily				Weekly				Monthly			
	Sunshine, per Cent	Units Ultraviolet Light	Rainfall	Temperature	Sunshine, per Cent	Units Ultraviolet Light	Rainfall	Temperature	Sunshine, per Cent	Units Ultraviolet Light	Rainfall	Temperature
Sept. 7	32	1.5	0	61								
8	67	2.0	0	64								
9	70	2.0	0	62								
10	40	1.5	0	62								
11	0	1.0	0.35	55								
12	13	1.0	0.23	60								
13	21	1.5	0.02	71	34.7	1.50	0.086	62.0				
14	15	2.5	T	66								
15	71	3.0	0	66								
16	86	4.0	0	78								
17	100	3.0	0	74								
18	42	3.0	0.03	64								
19	54	7.0	0	59								
20	100	7.0	0	67	67.0	4.20	0.004	68.0				
21	95	9.0	0	79								
22	93	6.0	0	84								
23	100	4.0	0	65								
24	50	4.0	0	65								
25	0	4.0	0.20	62								
26	9	2.0	T	60								
27	11	1.5	0	60	51.0	4.36	0.003	68.0				
28	6	1.0	T	56								
29	25	1.5	0	56								
30	5	1.0	0	64					45.0	2.88	0.021	64.8

† Trace.

* The first column represents the percentage of sunshine estimated from the number of hours of possible sunshine; the third column is the precipitation in inches from midnight to midnight, and the fourth column is the local temperature at noon. The table also gives the weekly averages by the day and the monthly averages by the day.

has to kill infusoria placed in a quartz cell. According to Hill,[12] "one unit of fading on the scale is equal to twice the infusoria-killing dose, and from two to four times the erythema dose, the sensitivity of the skin varying in individuals. The skin of the inner surface of the arm was used for the erythema dose." With the quartz tube containing the acetone-methylene blue solution placed 12 inches (30.5 cm.) from the mercury arc of a Burdick lamp (operated at 8 amperes and 75 volts), it took an exposure of ten minutes to reduce the standard solution 4 points. This means that at 12 inches, an erythema dose could be produced in from 37.5 to 75 seconds. At 24 inches, the same dose would require from two and one-half to five minutes and at 36 inches, from about five and one-half to eleven minutes. An erythema dose can be considered slightly in excess of a therapeutic dose, according to the data of Tisdall and Brown.[13]

By irradiating the standard solution in the quartz tube through a sheet of vitaglass, 2 mm. in thickness, it was found necessary to give an exposure of twenty minutes to get a reduction of 1.5 points. This means that the vitaglass cut out 81.25 per cent of the ultraviolet light. Similar measurements with helioglass showed that it took thirty minutes to get a reduction of 4.5 points. In this instance, 62.5 per cent of the ultraviolet light was cut out. Therefore, in order to get the same reduction with vitaglass as without it, about five times as much time must be allowed, and with helioglass about three times as much. These results were confirmed by finding that the time necessary to produce an erythema of the skin of the inner surface of the forearm corresponded to the foregoing results.

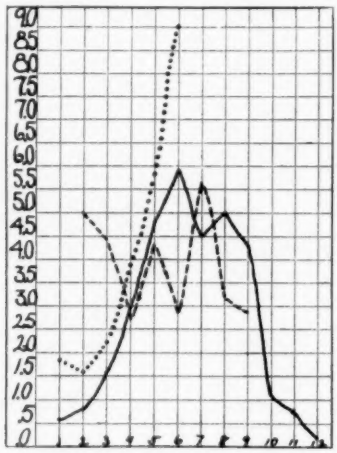

Chart 3.—The monthly average, by the day, of ultraviolet light in the sunshine of Portland, Ore. (broken line), Toronto, Ont. (dotted line), and London (solid line). The figures in the left hand column indicate units of ultraviolet light, according to the acetone-methylene blue scale. The figures at the bottom are for months of the year.

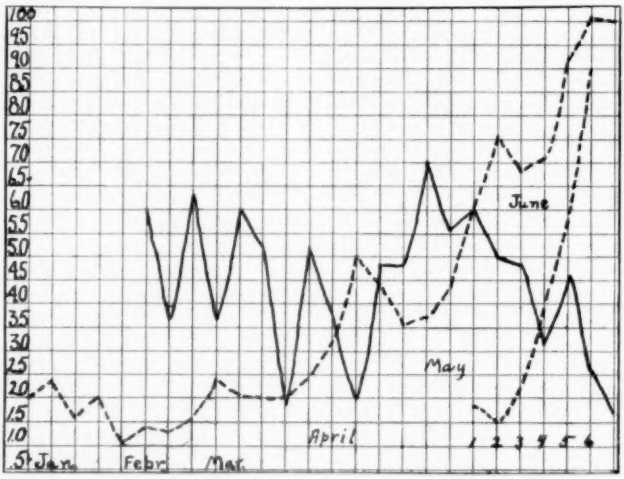

Chart 4.—The weekly average, by the day, of the amount of ultraviolet light in the sunshine of Toronto (solid line) and Portland, Ore. (dotted line), from January to July, 1927. It will be noted that for Toronto, the curve starts low, and for Portland, high, and that in April this relationship is reversed and thus maintained for the rest of the period. The amount for Toronto is shown by the solid line; the amount for Portland is indicated by the broken line, that at the left representing the daily average for the week, and that at the right, the daily average for the month.

Fleming [32] found that with a continuous exposure, the winter sunshine of Washington, D. C., provided enough ultraviolet light to promote normal calcification even when filtered through vitaglass. Tisdall and Brown [33] working in Toronto with exposures limited to two hours (from 11 a. m. to 1 p. m.) found that winter sunlight possessed a slight but definite antirachitic effect; that skyshine had one-half to two-thirds the effect of the sunshine (sunshine plus skyshine), and that through vitaglass there was no appreciable effect until March. A comparison of the curves for ultraviolet light in Toronto and in Portland for the same months, shown in charts 3 and 4, indicates that better results could be obtained here in the winter months than in Toronto and that poorer results would follow after the first of March.

From data so far collected, I believe that not less than half of the total ultraviolet light for one day is received between the hours of 10 a. m. and 1 p. m. Measurements for this period were undertaken with the belief that, all points being considered, it represented the best time of the day for solarization. If subsequent data should confirm the foregoing impression, it would be possible to work out a table as follows:

TABLE 3.—*Dosage of Ultraviolet Light, Based on the Total Amount for the Day*

Total Units Ultraviolet Light for Day	Units Received from 10 a.m. to 1 p.m.	Time Necessary for 1 Erythema Dose, Minutes		
		Sunshine*	Through Vitaglass	Through Helioglass
2	1.0	45 - 90	225 - 450	135 - 270
3	1.5	30 - 60	150 - 300	90 - 180
4	2.0	22.5- 45	112.5- 225	67.5- 135
5	2.5	18 - 36	90 - 180	54 - 108
6	3.0	15 - 30	75 - 150	45 - 90

* Sunshine plus skyshine.

From table 3 it will be seen that all those days in which there was a total of 2 or more units of ultraviolet light would be capable of furnishing a therapeutic dose if the irradiation were direct. When the light is filtered through helioglass, as it would be in a solarium glazed with this material, only those days having 3 or more units would be potent, while with a vitaglass filter the daily amount would need to be 5 or more units. It is assumed that the glass is kept scrupulously clean and is changed sufficiently often to insure its primary transmissibility.

32. Fleming, W. D.: Mil. Surgeon **62**:592, 1928.

33. Tisdall, Frederick F., and Brown, Alan: Antirachitic Value of Sun's Rays Through Various Special Window Glasses, Am. J. Dis. Child **34**:742 (Nov.) 1927; footnotes 15 and 25.

Table 4 has been prepared by arranging the thirty-three weeks recorded in table 2 according to the frequency of their daily averages:

TABLE 4.—*Frequency of the Daily Averages for Weeks Reported in Table 2*

Units Ultraviolet Light, Daily Average	Weeks	Months	Units Ultraviolet Light, Daily Average	Weeks	Months
2—	2	0	6+	4	0
2+	31	8	7+	2	0
3+	27	5	8+	1	0
4+	19	4	9+	1	0
5+	10	2	10+	0	0

Thus it will be seen that during most of the time of observation, definite therapeutic results could be expected from direct solarization for periods of exposure well within the three hours which were chosen as the ideal time of the day for irradiation. In solariums glazed with helioglass, solarization would be of value 80 per cent of the time, and in those using vitaglass benefit would be obtained only 30 per cent of the time.

If 4.34 units are considered the general weekly average (by the day), it will be found that the weeks with a lower average occur with equal frequency throughout the entire period under observation. The astonishing thing is that in over one half of the days of the summer period (June 21 to September 21) the rate falls below this average. Fortunately at this time of the year compensation is easily obtained by increasing the time of exposure. It should be kept in mind, however, that outside of the three hour limit, the time of exposure must be increased as rapidly as the amount of ultraviolet light decreases. In August, for example, when there were few days when the rate was more than 4 units (the average for the month being 3.22), the maximum time necessary to produce a therapeutic result was about one hour. At this period of the year, the time of the exposure could easily be trebled if necessary, but in a solarium glazed with vitaglass where the maximum time is already five hours, a threefold increase would be impossible.

The amount of ultraviolet light in the sunshine of Portland, Ore., as recorded for 1928, by the method here employed, does not mean that this is the total light available for biologic reactions. Low as the record is, it would be lower still if the readings were made in the city proper. At is was, the readings were made on top of the medical school building which is located on the summit of a small hill southwest of the city. The difference in elevation is about 300 feet but is sufficient to rise above much of the low lying fog and smoke. The readings thus obtained are undoubtedly greater than what would be obtained in the city proper. A further analysis would seem to make necessary another reduction in the amount of ultraviolet light here recorded. Hill, in the article to

which reference has already been made,[12] stated that "there is a minimal value below which no biologic reaction results, (*a*) for time, (*b*) for intensity of the source. While interrupted excitations, each below the threshold value, may be summated and provoke a reaction, with sufficient intervals such interrupted excitations become ineffectual." That such interruptions do occur is seen in the data of the U. S. Public Health Service.[19] They stated that on a clear day when small clouds pass over the sun, the illumination will fall in one minute's time from 9,000 or more foot candles to 3,000 or less and return as rapidly during the succeeding minute. An acetone-methylene blue may show fading during a period of twenty-four hours' exposure to weak and interrupted excita-

Chart 5.—The dotted areas are those reporting an amount of sunlight as low as or lower than that of Portland, Ore.

tions that would not be capable of producing any biologic result such as antirachitic activation of foodstuffs or elevation of blood phosphorus.[34] It is thus seen that while the readings for ultraviolet light in the sunshine of the area studied are very low, they probably will have to be reduced still further before they can be thought of in terms of biologic units.

A study of the quantity of sunshine recorded by the various stations of the Weather Bureau will show that the sunshine of Portland, Ore., as representative of the Northwest, is consistently exceeded in amount by all the stations except those found in Michigan, New York, Vermont,

34. With the Burdick lamp, summation results with two minute intervals of excitation.

Maine and the Ohio valley. Just how low Portland falls in this respect can be seen from the following table:

TABLE 5.—*Relation Between Amount of Sunshine Reported for Portland, Ore., and That for Other Stations*

Year	Number of Stations	Portland Among the Lowest	Per Cent
1926	163	36	22
1925	164	24	15
1924	165	22	14
1923	165	28	17
1922	165	23	14
1921	165	24	15
1920	165	37	23
1919	165	32	20
1918	162	22	14
1917	155	7	5
1916	153	6	4
1915	152	4	3
1914	148	5	4
1913	148	5	4
1912	136	3	3
1911	138	5	4
1910	138	4	3
1909	125	18	15
1908	137	11	8
1907	125	31	25

During the same period of time, that is, from 1907 to 1926 inclusive, the number of times that stations by states were reported as low as, or lower than, Portland, Ore., are as follows:

TABLE 6.—*Frequency with Which Stations Reported as Low Amounts of Ultraviolet Light as That for Portland, from 1907 to 1926*

State	Frequency	State	Frequency
Michigan	68	Iowa	5
Washington	59	Rhode Island	4
New York	45	Montana	4
Pennsylvania	21	Tennessee	3
Oregon	21	Texas (Del Rio)	2
Vermont	21	South Dakota	2
West Virginia	17	Wyoming	2
Ohio	14	Virginia	1
California (northern half)	11	Wisconsin	1
Juneau, Alaska	9	Massachusetts	1
Kentucky	8	North Carolina	1
Maine	7	Alabama	1
Indiana	6	Louisiana	1
Connecticut	5	Minnesota	1

In table 6, all the states as far down the list as Connecticut can be grouped as already outlined, with the exception of Juneau, Alaska. The remainder can be considered as appearing in the list only because of occasional low records. A map of the United States, stippled in such a way as to represent the data contained in the foregoing tabulation, graphically portrays the division already mentioned (chart 5).

For further comparison, Cincinnati, O., may be considered a representative station for the Ohio Valley; Atlanta, Ga., for the South; Portland, Me., for the New England states; Bismarck, N. D., for the North Central states; Yuma, Ariz., for the Southwest, and Portland,

Ore., for the Northwest. A graphic representation of the monthly and annual averages for sunshine in these areas is found in chart 6. It also furnishes the material for the following summary:

TABLE 7.—*Periods of More than the Average Amount of Sunshine for Six Representative Stations*

Station	Annual Average, per Cent	Months Above the Average, Inclusive	Months Above the Average, Inclusive
Yuma, Ariz.	90	March to November	December to February
Altanta, Ga.	59	April to November	December to March
Bismarck, N.D.	59	April to October	November to March
Portland, Me.	58	May to October	November to April
Cincinnati	55	May to October	November to April
Portland, Ore.	50	April to September	October to March

It might be contended that the amount of sunshine reported for Portland, Ore., for 1928 does not represent an average year's total amount of sunshine. Chart 7 seems to bear out this contention, for there it will be observed that the average amount of sunshine for a period of thirty-five years for the months under consideration is 54 per cent, while that for 1928 is only 48 per cent, a decrease of 11.1 per cent. If one considers the average deviation from the mean (9.4 per cent), however, it will be found that the average for the year 1928 departs from this by only 1.7 per cent. At the same time, the maximum deviation was found to occur during the year 1917 (22 per cent) and the minimum during 1908 (0.9 per cent). The year 1928, therefore, is far from being an extreme year and varies from the average for thirty-five years by less than 2 per cent.

Charts 2, 8 and 10 will show that the ultraviolet light of sunshine is directly correlated to the amount of sunshine and that, in general, there is a reciprocal relationship between it and rainfall. There seems to be no correlation between the temperature and the amount of ultraviolet light. As a rule the curve for ultraviolet light parallels that for the amount of sunshine. However, it must be noted that for February and March the relative amount of ultraviolet light is greater than the amount of sunshine. In April this relationship is reversed; from then on, this relationship is maintained except for variations in the width of the zone between the two curves. An explanation of these two variations will be of interest. The greater relative amount of ultraviolet light in February and March than in the other months here reported is probably due to the ultraviolet value of skyshine. During that time of the year in this district the air is comparatively free from fog and smoke so that, although the sky is frequently overcast with clouds, much of the ultraviolet radiation of the sun is capable of reaching the earth's surface. After April, the amount of smoke in the air increases. Farmers, homesteaders and others select this time of the year, as well

as the fall after the first rains, to burn their slashings. During the summer months the amount of smoke in the air steadily increases and is due for the most part to forest fires. The width of the zone in May and August can be explained as being due to the absorption of ultraviolet rays by the smoke. The narrowness of the zone in the latter

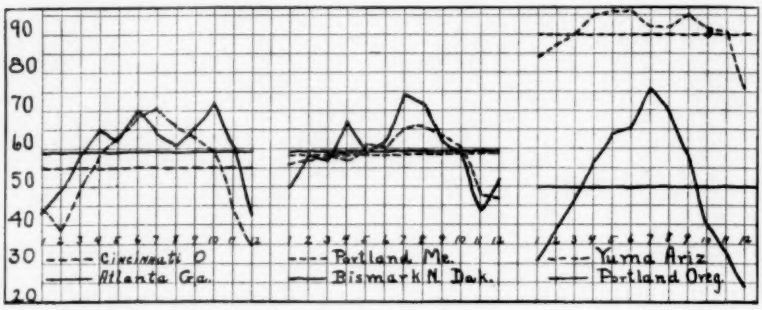

Chart 6.—The monthly and annual average of sunshine, by the day, in six cities, representing the Ohio valley, the South, New England, the north central, southwest and northwest areas of the United States, for the years 1920 to 1926, inclusive. The horizontal lines show the annual averages for the respective areas.

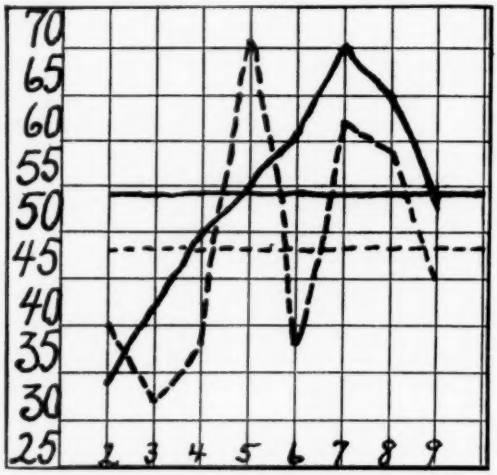

Chart 7.—The amount of sunshine received in Portland, Ore., during a period of thirty-five years (solid line), as compared with the amount received in 1928 only (broken line). February to September, inclusive, are the months reported. The monthly average by the day, and the total average by the day are contrasted.

part of March and April is undoubtedly due to the effect of the rainfall in clearing the atmosphere of smoke.

In chart 9, the weeks having a daily average over 4.34 units of ultraviolet light are numbered above the line and those below this

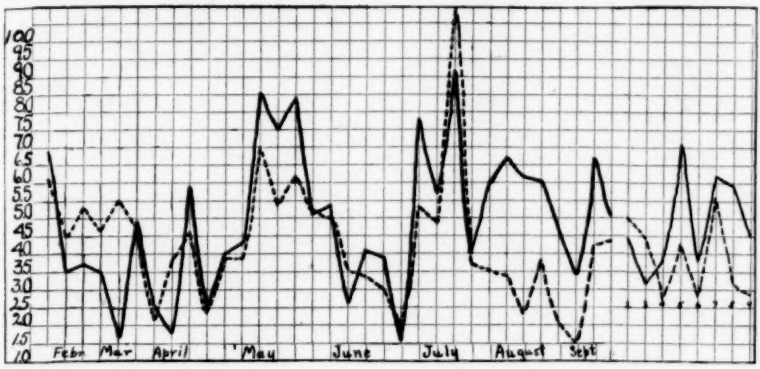

Chart 8.—The weekly average, by the day, of the sunshine (solid line) and of the amount of ultraviolet light (broken line) for the period from Feb. 10 to Sept. 28, 1928. The figures in the left hand column, representing the units of ultraviolet light, can be read as percentage of sunshine by disregarding the decimal point. The curves at the right show the monthly averages by the day.

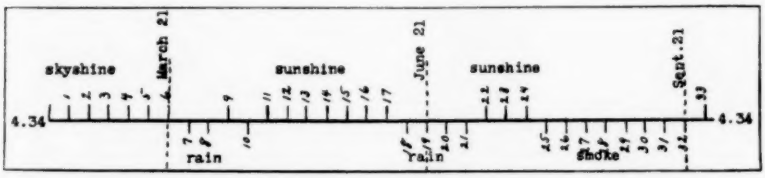

Chart 9.—The relative number of weeks having more or less than a daily average of 4.34 units of ultraviolet light. The figures above the line represent the weeks with more than the average amount; those below, the weeks with less.

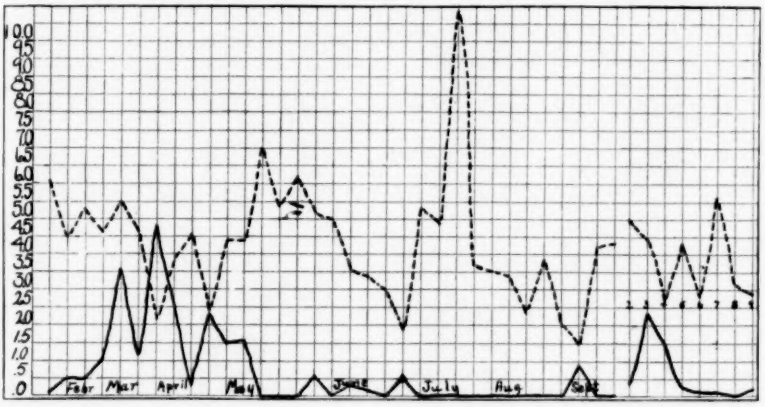

Chart 10.—The weekly average, by the day, of the rainfall (solid line) and of the amount of ultraviolet light (broken line) for the period from Feb. 10 to Sept. 28, 1928. The figures in the left hand column, which represent units of ultraviolet light, should be read as hundredths of an inch, disregarding the decimal point. The curves at the right show the monthly averages by the day.

average are numbered below the line. In the entire period of thirty-three weeks there are eighteen weeks averaging over 4.34 units, and fifteen weeks averaging less than this. If the totals are taken for the spring and summer quarters, it will be found that during the spring there were eight weeks above the average and five below, and for the summer, three above and ten below. The marked contrast between the steady and pronounced increase of ultraviolet light in the sunshine of London and of Toronto (charts 3 and 4) as midsummer approaches, as compared to the inconstant, low and fluctuating values for this district, emphasizes the degree to which the sunshine of this area has been devitalized by smoke. With an annual average of sunshine of only 50 per cent and with this markedly reduced in its ultraviolet content during those months of the year when there should be a natural increase, one can realize to some extent the necessity for more accurate quantitative data as well as information concerning the methods available for compensating for this deficiency.

TABLE 8.—*Incidence of Forest Fires in Oregon and Washington for 1927 and 1928*

Year	Total Number of Fires	Caused by Man	Not Caused by Man
1927	1,536	424	1,112
1928	1,350	772	578
Total	2,886	1,196	1,690

The United Forest Service reports [35] that for 1927 and 1928, the number of forest fires in the National Forest Reserves of Oregon and Washington were as shown in table 8.

The curve obtained by plotting the number of fires reported for ten day periods throughout the 1928 season can be seen by referring to chart 11. There it will be observed that the curve has the same general conformation as the one for sunshine so that if it were superimposed on chart 8 the reason for the wide zone occurring in August between the curve for sunshine and that for ultraviolet light would become apparent. The amount of smoke present in the Northwest because of 1,350 or 1,536 forest fires becomes still more impressive when it is realized that these figures do not include those from forest areas under private protection, smoke from burning slashings, saw-mill dumps and industrial areas. The Forest Service feels so strongly about the subject that a vigorous educational program is being undertaken calculated to arouse sufficient interest that measures will be instituted to bring about an abatement in the nuisance. Their propaganda is based on five points, namely: (*a*) inability of forest patrol observers to make accurate observations because of the smoke screen; (*b*) curtailment

35. Personal communication.

in the effectiveness of aeroplane fire patrol; (*c*) danger to commercial aviation; (*d*) ineffectiveness of tourist propaganda when the scenic beauties pointed out are obscured by smoke and (*e*) failure of crops to properly mature because of lack of sunlight. (Wenatchee apple orchardists, for example, stated that they lost thousands of dollars this season because of the failure of the apples to develop their proper color.) Another important point can be added: namely, that a naturally low

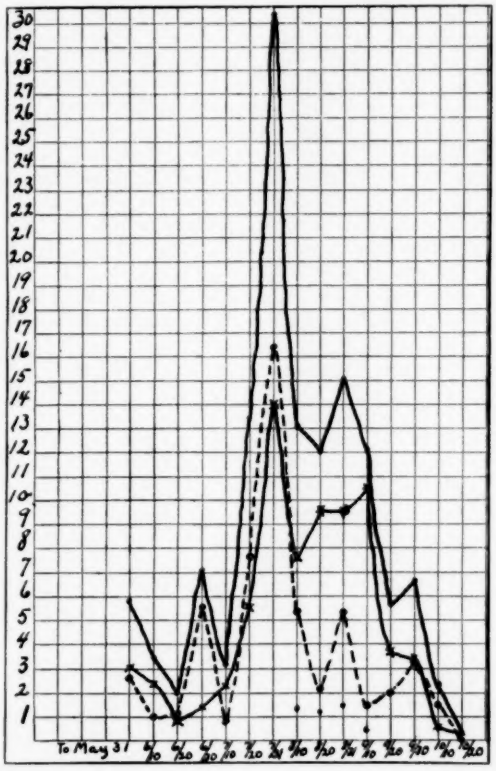

Chart 11.—The number of forest fires in Oregon and Washington reported at ten day intervals during 1928. This does not include data from forested areas privately owned and protected, which probably should not affect the record of seasonal incidence. The curve traced by the solid line shows the total number of fires; by the solid line and crosses, the number which man caused, and by the broken line, the number which were not caused by man.

amount of ultraviolet light, with its benevolent influence on animal and plant life, is reduced still further in quantity.

Granted, then, that the amount of the ultraviolet component of sunshine in the Northwest is naturally low and that it is still further reduced by the excessive pollution of the air by smoke, fog and dust, the ques-

tion arises as to the methods available for effectively combating or compensating for this deficiency. Without a too detailed discussion of this aspect of the situation, let it be said that there are several lines along which considerable work can be accomplished.

From the figures given for the number of forest fires during the last two years, it is obvious that if the Forest Service is given adequate support, measures can be initiated that will reduce the smoke menace from forest fires by nearly 50 per cent. It is also possible to control the smoke in industrial areas.

The relative mildness of the climate in the Northwest should permit of greater freedom in the style of dress. Man has not yet compensated for the deficiency of ultraviolet light in the sunshine of the temperate zone; in order to prevent undue losses of heat he has clothed himself in such a manner that a poor condition is made worse. However much has been said against the modern styles in women's dress, it must be admitted that they allow much more exposure of the skin to the beneficial action of the sun and air than is permitted by the prevailing modes for men. It has been shown that certain fabrics possess the power of greater transmissibility to ultraviolet radiations than others.[36] It would therefore seem that a more intelligent adjustment to styles and choice of fabrics would have considerable influence in alleviating the condition of shortage of ultraviolet light.

While a more determined effort to benefit by outdoor irradiation either by actual exposure or exposure permitted by modified dress can do much good, the benefit to be derived from irradiated foods should not be overlooked. In this connection, it would be wise to keep in mind a strict supervision of the selection of foods. Preference should be given to fieldgrown crops unless greenhouses install mercury vapor lamps or other sources of ultraviolet light or glaze their buildings with glass that is permeable to these rays; to foods shipped in from the districts that are not so limited in sunshine rich in the shorter wave lengths, and to foods deliberately irradiated by ultraviolet light.

Too much confidence must not be placed in the efficacy of various window glasses to transmit the shorter wave lengths found in the spectrum of the sun. Fleming [32] has shown that when vitaglass, one of the best of these materials, is exposed to the weather in Washington, D. C., from Dec. 12, 1927, to March 26, 1928, its original transmissibility of 47 per cent is decreased to 34 per cent, in the case of clean glass, and 21 per cent for dirty glass. The Bureau of Standards found that the complete degeneration of vitaglass by the mercury arc reduced its transmissibility to 25 per cent and that further exposures to either sun-

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36. Dozier, C. C., and Morgan, H.: Am. J. Physiol. **84**:603, 1928. Morgan, H.: Am. J. Physiol. **86**:32, 1928.

light or the mercury arc caused no further decrease. It is therefore evident that unless window glass substitutes are cleaned frequently and replaced every two or three months, their ability to transmit ultraviolet light will shrink from less than one half to one fourth or even more.

As far as calcium and phosphorus metabolism are concerned, vitamin D seems to be the ultimate form in which ultraviolet light is utilized by the body. There appears to be a certain limit in the ability of the irradiation of the skin to alter the level of blood calcium or phosphorus because of the development of a pigment characteristic of tanning. This pigment production is Nature's method of protecting the human organism against excessive amounts of ultraviolet irradiation. On the other hand, also, Nature seems to have set an upper limit to the ingestion of vitamin D by making it quite scarce in natural foods. The general shortage of vitamin D in foods is adequately compensated for in the tropics by the abundance of the shorter wave lengths in the sunlight. Furthermore, as already mentioned, there is no danger of overcompensation and, because of the adequacy of sunlight, there is no call for an increased ingestion of foodstuffs rich in vitamin D. This is not true for those areas in which both the food and sunlight are deficient. Thus, when the dark skinned races are transplanted from their natural habitat to regions where there is less sunshine they immediately become more susceptible to a deficiency in ultraviolet light than the white-skinned races.[37] Increases can be brought about in irradiation, both natural and artificial, with no more danger of overstimulation than existed in the aforementioned conditions. In the tropics, irradiation is obtained without any effort or expense. This is not true in the areas of deficiency. The resulting condition is that an increase in the ingestion of substances containing vitamin D offers as good an alternative as seeking or obtaining more ultraviolet irradiation. Now that it is possible to produce vitamin D and ultraviolet light at will, it has become exceedingly easy to exceed those limits beyond which Nature has never gone. While it is not superficially apparent that much harm can arise from the prolonged use of ultraviolet irradiations by normal people, there are some pathologic conditions in which it is definitely contraindicated. Too much emphasis, therefore, cannot be placed on the undesirability of allowing the promiscuous use of ultraviolet lamps or the uncontrolled dispensing of such highly potent preparations of vitamin D as activated ergosterol. Nor can the warning be made too forcible that definite contraindications exist to the excessive use of these therapeutic modalities.

In the irradiation of foods, the following facts should be kept in mind: (*a*) vitamin A may be destroyed; (*b*) vitamin D may be inactivated and, hence, cannot be reactivated; (*c*) it may be possible to

37. Hess, A. F.: Am. J. Pub. Health. **12**:104, 1922.

eliminate objectionable features such as the bad taste developed in irradiated milk, by irradiation in an atmosphere of carbon dioxide.[38]

These measurements are being continued so that a period of twelve months will be included. Furthermore, readings are made at 10 a. m. and 1 p. m. so that data will be available to show what part of the daily total will fall within this period. This material will form the substance of a future report.

CONCLUSIONS

1. Portland, Ore., as a representative locality of the Northwest, has the lowest annual average of sunshine of all areas in the United States. Michigan, Main, Vermont, New York and the Ohio Valley receive almost as low a percentage.

2. Plotting the curve for ultraviolet light against that of temperature, rainfall and sunshine shows that the closest correlation exists between ultraviolet light and sunshine, the least between it and temperature and that a possible inverse relationship exists between ultraviolet light and rainfall.

3. The readings for 1928 cannot be vitiated by the fact that it appears to be a year usually low in sunshine, for two reasons: (1) the deviation of the average for 1928 from the average for the preceding thirty-five years is well within the maximum and minimum deviation (22 per cent and 0.9 per cent); and (2) the average for 1928 deviates from the mean of the preceding thirty-five years by only 1.7 per cent, the average deviation being 9.4 per cent.

4. Instead of the amount of ultraviolet light gradually increasing as the months progress, as occurs in London and Toronto and as one would expect from the gradual increase in the amount of sunshine, there is an extreme fluctuation, so that only one month (July) shows a higher average than February.

5. The pall of smoke hanging over the Northwest during the late spring, summer and early fall is considered more of a menace than a nuisance.

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38. Scheer, K.: München. med. Wchnschr. **75**:642, 1928.

AN EXPERIMENTAL STUDY OF CHRONIC FATIGUE

PART II *

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AND
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In 1923, in a paper called "Physiology of Exercise," [1] we presented the results of a study of the physical capacity of children by means of a stationary bicycle. It was then pointed out that a considerable number of supposedly normal children fell below the average in physical strength and endurance. This striking observation led us to an inquiry into the psychophysiologic aspects of general subefficiency. The results were published in a paper called "Chronic Fatigue in the School Child: A Psycho-Physiologic Study." [2]

Since clinical methods of investigation offer little hope for the understanding of the nature of fatigue, we undertook to study this subject in animals. In this paper, we shall discuss the effect of forced exercise on (1) the voluntary activity, (2) the weight and (3) the behavior of rats.

MATERIAL AND EXPERIMENTAL PROCEDURE

Twenty male hooded rats, about 90 days of age, weighing on an average 250 Gm., were selected. Each rat was kept in a revolving cage made of wire net and equipped with pedometer to record the daily activity of the animal. The cages were arranged in two rows, each row holding five cages. Ten of the cages were attached to a motor by means of a pulley. Either one or both rows simultaneously could be set in motion. Each cage was connected with the other by means of elastic ribbons 1 inch (2.5 cm.) in width. While the upper cages were driven directly by the force of the motor, motion was transferred to the lower ones by means of a shaft from which an elastic ribbon ran to the pulley. Immediately after exercise the ribbons were slipped off the cages so that there was no interference with the voluntary activity of the rats during the remainder of the day.

Each morning at the same time the voluntary activity was determined by comparing the reading on the pedometer with that of the previous day. Then each rat was weighed to get the daily gain. Food was distributed two hours later. The

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* From the Department of Pediatrics, University of Minnesota.

* Work done through a grant given by Dean G. S. Ford of the Graduate School of the University of Minnesota.

1. Seham, Max and Seham, Grete: Physiology of Exercise, Am. J. Dis. Child. **26**:254 (Sept.) 1923.

2. Seham, Max: Chronic Fatigue in the School Child, Boston M. & S. J. **194**:770 (April) 1926.

food consisted of one eighth of a pound (56.7 Gm.) of white bread soaked in whole milk. Thus each rat was assurred of a sufficient quantity of food to last him through the day.

Ten rats were kept in revolving cages but were not subjected to exercise, while the other ten rats were subjected to exercise on the seventeenth day. The exercise last from thirty to sixty minutes a day, and the speed varied from fifteen revolutions per minute to thirty revolutions during the last eight days of the experiment. The exercise period was followed by a period of seventeen days in which the after-effects of fatigue and the rapidity of recovery were studied.

The experimental difficulties were twofold:

1. As soon as the motor was started, some of the rats would take to the shaft which ran through the center of the cage. By increasing the diameter of the shaft to 1 inch (2.5 cm.) by means of electric tape, this difficulty was overcome in all but one rat (rat 9).

TABLE 1.—*Voluntary Activity of Control Rats*

	Rat 1	Rat 2	Rat 3	Rat 4	Rat 5	Rat 6	Rat 7	Rat 8	Rat 9	Rat 10
Before exercise										
12 days.....	2,234	13,165	.....	10.7	608.5	1,154	1,221	10.9	410	3,246
During exercise (37 days)										
1st 7 days.....	3,608	10,886	1,231	4	417	28	1,035	9.7	523	3,443
2d 7 days.....	3,997	5,117	3,429	6.5	336	81	1,928	9.7	827	2,942
3d 7 days.....	4,003	4,749	5,756	6.7	406	9	3,491	9	330	3,034
4th 7 days.....	1,995*	4,449	5,182	6.7	185	6	2,828	6.3	269	2,797
5th 7 days.....	†	3,169	10,542	4.4	233	3.1	3,640	5.3		3,746
Last 2 days....	†	1,976	8,036	7.2	83	2.5	4,011	6.5		†
After exercise										
1st 7 days.....	†	1,799	3,938*	7.3	91	2.7	1,236*	2.7	97	303
2d 7 days.....	876*	879	2,030	3.71	76	5.3	3,182‡	6.3	73	1,223
Last 2 days....	635*	1,791	995	0.5	18	2.5	1,164	1.5	54	485

* indicates six days only.
† indicates out of order.
‡ indicates five days only.

2. The roughness of the wire net of which the cages were made caused bleeding of the feet in four of the ten exercised rats. How far bleeding affected the final results will be discussed in a later part of this paper.

COMPARISON OF THE VOLUNTARY ACTIVITY OF CONTROL RATS AND OF EXERCISED RATS

Table 1 shows the voluntary activity of the control rats. The first column indicates the three periods into which the experiment was divided and the number of days in each period. In the other columns one finds the number of revolutions representing the average of the daily activity for each seven days and for the last two days, respectively.

Table 2 shows the effect of forced exercise on voluntary activity. The two tables are the same except for the column containing the average number of revolutions of forced exercise.

A comparison of the voluntary activity of the control rats for the first twelve days and for the latter part of the exercise periods shows that the voluntary activity remains practically the same throughout the experiment. This cannot be said of the exercised rats. Here we find that the longer the exercise period the greater the decrease in the voluntary activity. For instance, for rat 1 the voluntary activity drops from 423 to nine revolutions during the last two days and for rat 2 from 3,102 to six revolutions.

TABLE 2.—*Effect of Forced Exercise on Voluntary Activity*

	Rat 1		Rat 2		Rat 3		Rat 4		Rat 5	
	Voluntary Activity	Forced Exercise	Voluntary Activity	Forced Exercise	Voluntary Activity	Forced Exercise	Voluntary Activity	Forced Exercise	Voluntary Activity	Forced Exercise
Before exercise										
10 days.....	423	.....	3,102	.....	260	.....	2,759	.....	1.372	.....
During exercise										
1st 7 days.....	213*	578	1,460*	578	254	579	2,740	579	1,262	594
2d 7 days.....	287*	1,017	690†	1,045*	241†	1,017	2,136*	1,078*	626*	1,107*
3d 7 days.....	85*	991	291‡	1,004*	207*	1,022	1,559†	1,031	400*	1,056*
4th 7 days.....	50.5	1,333	775*	1,345	22.4	1.394	321	1,723	193	1,502
5th 7 days.....	49	2,426	390	1,840	45.3	2,515	5.1	2,727	.....	.....
Last 2 days....	9	2,779	6	2,006	711	2,649	3	2,735	1.5	1,903
After exercise										
1st 7 days.....	133	.....	1,295*	.....	630	.....	482*	.....	.....	.....
2d 7 days.....	57	.....	1,219*	.....	564	.....	393	.....	.....	.....
Last 2 days....	16.5	.....	1,214	.....	206	.....	498	.....	.....	.....

	Rat 6		Rat 7		Rat 8		Rat 9		Rat 10	
	Voluntary Activity	Forced Exercise	Voluntary Activity	Forced Exercise	Voluntary Activity	Forced Exercise	Voluntary Activity	Forced Exercise	Voluntary Activity	Forced Exercise
Before exercise										
10 days.....	4,209	.....	3,044	.....	2,919§	.....	4,944	.....	4,325	.....
During exercise										
1st 7 days.....	3,160*	638	3,382§	640	936*	631	6,352†	636	4,952	669
2d 7 days.....	1,948*	921*	4,038*	1,092*	1,238*	1,083*	7,408¶	1,091*	3,749*	1,079*
3d 7 days.....	2,308†	1,291*	3,030	1,500*	701*	1,446*	9,051*¶	1,399*	5,805*	1,400*
4th 7 days.....	120†	1,204	1,201	1,880	946	1,951	2,331	2,004	4,556*	2,023
5th 7 days.....	21	1,901	710	2,631	939	2,393	5,363	2,371	4,809	2,314
Last 2 days....	.....	.....	24	2,810	.....	2,530	208	2,714	7	2,553
After exercise										
1st 7 days.....	1.9*	.....	1,796	.....	.....	.....	1,584	.....	1,928	.....
2d 7 days.....	486	.....	347*	.....	.....	.....	1.437	.....	3,599	.....
Last 2 days....	186	.....	469	.....	.....	.....	1,551	.....	3,598	.....

* indicates six days only.
† indicates five days only.
‡ indicates three days only.
§ indicates nine days only.
¶ indicates that the animal did not get enough food.

The after-effect of exercise on voluntary activity could not be established because even the control rats seemed to undergo a reduction in activity during that period. This was probably due to age.

EFFECT OF FORCED EXERCISE ON THE WEIGHT OF RATS

As mentioned before, each rat was weighed every day. During the last three days of the experiment, the exercised rats were weighed before and after exercise. The effect of exercise on weight is well brought out

in table 3, in which the gain in weight of the exercised rats is compared with the gain in weight of the control rats. We found that in the pre-exercise period both groups gained readily; as a matter of fact, the exercised rats were in the lead. The average gain in weight for the exercised rats was 32.1 Gm. against 27.1 Gm. for the control rats. But during the exercise period the figures reverse themselves. For instance, control rat 2 gained 72.7 Gm., while exercised rat 2 gained only 27.8 Gm. Again, against the average gain of 61.9 Gm. in the control rats, we have an average gain of only 17.2 Gm. in the exercised rats. It is interesting to note that the gain in weight reverses itself again in the after exercise period, the exercised rats gaining twice as much as the control rats.

TABLE 3.—*Comparison of Gain in Weight in Control and Exercised Rats*

	Control Rats			Exercised Rats		
Rat	Before Exercise, Gm.	During Exercise, Gm.	After Exercise, Gm.	Before Exercise, Gm.	During Exercise, Gm.	After Exercise, Gm.
1	34.7	....	....	34.5	20.3	4.0
2	13.6	72.7	33.0	42.3	27.8	44.6*
3	....	76.5	42.7	28.2	32.8	24.9
4	37.2	69.3	24.9	34.0	33.6	35.6
5	25.8	51.4	17.3	14.8	—10.0	Died†
6	30.9	41.6	5.8	33.5	— 7.6	49.9‡
7	....	75.8	1.5	37.8	29.1	35.4
8	....	52.9	—0.1	38.1	11.7	6.7
9	23.7	60.8	13.6	28.4	10.0	20.2§
10	24.0	56.3	12.1	29.2	26.0	38.4
Average	27.1	61.9	15.7	32.1	17.2	29.0

* Feet bleeding on thirty-first day.
† Feet bleeding on twenty-seventh day.
‡ Feet bleeding on twenty-ninth day.
§ Feet bleeding on thirty-fifth day.

As mentioned before, the rats were weighed before and after exercise during the last three days of the experiment. We thus learned that some of the rats lost so much in weight during exercise that their weight dropped below that of the previous day. Furthermore, they were not able to regain during the following day what they had lost during exercise.

One might make the objection that the low average gain of the exercised rats may be due to the bleeding of the feet of some of the animals. Since none of the rats began to bleed until the twenty-seventh day, we thought it advisable to calculate how much each rat had gained up to that time (table 4). Here, again, we find a considerable decrease in the gain of weight in the exercised rats. The average gain in weight of the latter is 25.3 Gm. against 52.6 Gm. in the control rats.

EFFECT OF FORCED EXERCISE ON BEHAVIOR

Apparently, forced exercise had a definite effect on the attitude of the rats toward the attendant. While in the beginning the rats showed no fear when being handled, toward the end of the experiment the attendant found it necessary to wear gloves as a protection against biting. The rats also exhibited a greater sensitiveness to noise, clapping of the hands startling them considerably. The restlessness of the rats was

TABLE 4.—*Comparison of Gain in Weight in Control and Exercised Rats Up to the Time of Bleeding*

	Average Gain in Weight in Grams	
	Control Rats	Exercised Rats
Rat 1	51.5	9.6
Rat 2	60.6	52.6
Rat 3	71.5	23.1
Rat 4	61.3	35.5
Rat 5	40.3	13.7
Rat 6	33.3	28.5
Rat 7	60.3	27.5
Rat 8	46.1	8.7
Rat 9	52.7	15.3
Rat 10	48.2	37.7
Average	52.6	25.2

TABLE 5.—*Study of Restlessness in Rats*

		Exercised Rats		
	Control Rats During 68 Days	Before Exercise	During Exercise	After Exercise
Rat 1	—	—	—	—
Rat 2	—	—	+++	+ bites
Rat 3	Lack of food	—	++	—
Rat 4	—	—	+	—
Rat 5	—	—	+	Died
Rat 6	—	—	+	—
Rat 7	—	—	++	++ bites
Rat 8	—	—	+	—
Rat 9	Twirled (11th to 25th day)	—	+	—
Rat 10	—	—	+	+ bites

best shown during weighing. In the beginning they remained quiet in the cage, but later on they became restless and tried to open the cage. The study of restlessness is tabulated in table 5. The control rats showed practically no restlessness. In the exercised rats, on the other hand, there was a marked increase during the period of exercise.

In the paper on the effect of undernutrition on voluntary activity, we reported a similar restlessness in undernourished rats. But in the latter this restlessness was only the symptom of their general hyperkenesis. In the exercised rats, however, this restlessness was rather in the nature of listlessness and irritability and was not a symptom of an actual increase in the capacity for work.

The restlessness of exercised rats expresses itself also in blinking. Normal rats blink little, if at all. Table 6 shows the comparative study of blinking in control and in exercised rats. (Control rat 2 suffered from an inflammation of the eye which accounts for the high number of blinks.) Each rat was observed for fifteen seconds every day. Blinking became more frequent the longer the exercise continued.

GROSS AND MICROSCOPIC ANATOMIC STUDIES

Five rats of another series died during the exercise period. For two weeks before death, they showed dangerous symptoms of exhaustion such as subnormal temperature, marked flaccidity, apathy and lack of

TABLE 6.—*Comparison of Blinking in Control Rats and Exercised Rats*

			Number of Days																	
			Exercise Period											After Exercise						
	Rat	Before Exercise	2	5	10	11	19	20	23	21	33	34	36	37	1	2	3	5	7	10
Control	1	..	10	..	..	..	..	..	..	..	..	4	..	..	5	15	8	..	..	..
	2	..	4	..	..	10	..	..	..	..	..	..	..	..	..	..	..	..	2	..
	3	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	4	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	5	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	6	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	7	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	8	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	9	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	10	..	..	..	..	..	..	..	3	..	..	..	..	..	..	..	..	..	..	..
Exercised	1	..	2	..	..	..	..	..	..	..	..	6	..	1	..	..	..	..	..	..
	2	..	3	..	..	..	..	..	..	..	..	..	..	2	5	..	..	..	1	2
	3	..	..	..	..	..	..	..	..	..	3	1	4	5	2	..	2	..	3	..
	4	..	1	..	1	1	3	3	..	..	1	5	1	3	2	5	1	4	..	..
	5	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	6	..	1	..	..	..	..	..	..	..	..	2	2	..	2	..	..	..	..	..
	7	..	1	..	..	..	..	..	..	..	..	2	..	..	..	2	..	..	..	..
	8	..	1	2	..	..	..	..	..	..	..	1	..	5	2	2	..	1	12	..
	9	..	1	5	..	..	..	..	..	..	..	3	..	..	4	..	..	..	..	..
	10	..	..	..	..	..	..	..	..	..	..	..	1	8	1	..	..	..	1	..

muscle tone. In all but one rat (rat 7), there was no hemorrhage in any of the organs. None of the hearts was dilated. This would mean that death was not due to any gross anatomic changes (table 7).

Before reporting on the results of the microscopic studies, we shall give a short account of similar work done in the past. Hodge,[3] in 1894, by studying the effect on sparrows of a day's flight, found that the Nissl bodies in the nerve cells showed protoplasmic changes. Dolley and Crile [4] subjected dogs to continuous exercise for from one to four hours and also noticed an increase in the size of the nerve cells of the brain and changes in the relation between the nucleus and the cytoplasm of the cells. Kocher and Lambert,[5] on the other hand, using the same

3. Hodge, C. L.: J. Morphol. **9**:449, 1894.

4. Dolley, D. H., and Crile, G. W.: J. Exper. Med. **8**:713, 1906.

5. Kocher, R. J.: Effect of Activity, J. A. M. A. **67**:278 (July 22) 1916. Lambert, M. M.: Compt. rend. Soc. méd. **44**:879, 1893.

material and about the same technic, were unable to find any such changes. The authors used rabbits free from any defect or diseases. Bast and Loevenhart [6] produced exhaustion in rabbits by keeping them from falling asleep. They asserted that in exhausted rats the cells of the spinal cord show a decrease in the chromatin material of the nuclei. They also found chromatolysis, which is characterized by granular Nissl bodies and the presence of vacuoles in the cytoplasm. There were also present pathologic changes in the medulla as could be seen in the chromatolysis in the rectangular formation and the dorsal nucleus of the spinal cord. The chromatolysis was the same as in the cells of the spinal cord. The motor nerve cells supplying somatic musculature showed no changes.

TABLE 7.—*Autopsy Analysis of Five Exhausted Rats* *

Rat	Sex	Heart Weight, Gm.†	Wistar Norms	Body Weight, Gm.	Comment—Condition of Viscera
1	M	0.61	0.607	138	Heart appeared normal (not distended with blood) (atria filled; ventricles nearly empty); lungs normal; abdominal viscera appeared normal; (gastrointestinal contents small in amount); brain appeared grossly normal
10	M	0.51	0.536	119	Heart appeared normal; condition same as in rat 1; lungs normal; abdominal viscera appeared normal; gastric contents slight; brain appeared grossly normal
4	M	0.45	0.460	96	Heart appeared normal; right atrium distended, otherwise nearly empty; lungs appeared normal (aside from postprandial congestion); abdominal viscera appeared normal, except intestinal distention with gas (postmortem ?); brain appeared grossly normal
3	M	0.51	0.507	109	Same in general as preceding rat; both atria filled (not distended); lungs appeared normal; intestines not gas-distended; viscera normal; brain appeared grossly normal
9	M	0.56	0.567	126	Same as rat 3, except brain, which showed large, recent subdural blood clot on dorsal aspect of brain at junction of cerebral hemispheres and cerebellum; meninges in general congested

* Work done by Prof. C. M. Jackson of the Department of Anatomy, University of Minnesota.

† All heart weights were within the range of normal variation; all were within 5 per cent of the Wistar norm for body weight.

Five of our animals of another series were killed by decapitation on Sept. 23, 1927, beginning at 3 p. m., in the following order: I-2, V-2, IV-7, IV-6, V-6, IV-2, II-4, IV-8, i. e., an experimental animal alternating with a normal animal. The brain and spinal cord were removed immediately and weighed and then put in a saturated aqueous solution of corrosive sublimate in 10 per cent solution of formaldehyde. The brain and cord of each animal were kept in a perforated vial, and all vials were kept together in the same large dish of reagent in all stages of the technic. Sections from the motor cortex, cerebellum and medulla

6. Bast, T. H., and Loevenhart, A. S.: Studies in Exhaustion Due to Lack of Sleep, Am. J. Physiol. **82**:121, 1927.

oblongata, and 6 cc. of segment of the spinal cord were cut. Five microns and one section of a given region from each animal were mounted on the same slide for staining, as follows:

V	IV	IV	IV	IV
2	7	6	2	8
	V	V	V	V
	2	5	6	4

Hence, the sections from all the animals were stained alike. About a dozen such slides were prepared from each region of the nervous system already mentioned. Sections were stained with different degrees of intensity for Nissl granules.

TABLE 8.—*Histologic Examination of Exhausted Rats* *

Number	Weight of Brain, Gm.	Weight of Spinal Cord, Gm.	Total Weight of Nervous System	Number	Weight of Brain, Gm.	Weight of Spinal Cord, Gm.	Total Weight of Nervous System
I-2.....	1.630	0.503	2.133	V-2.....	1.694	0.580	2.274
IV-7.....	1.668	0.515	2.183	V-5.....	1.707	0.549	2.256
IV-6.....	1.661	0.468	2.129	V-6.....	1.764	0.495	2.259
IV-2.....	1.524	0.454	1.978	IV-4.....	1.795	0.544	2.339
IV-8.....	1.721	0.610	2.331				
Total.....	8.204	2.550	10.754	Total.....	6.960	2.168	9.128
Average....	1.641	0.510	2.151	Average....	1.740	0.542	2.262
Average weight in experimental animals.....					1.641	0.510	2.151
Difference in weight between experimental and normal in favor of normals					0.099	0.032	0.131
Loss of weight by experimental animals in per cent of normal weight					5.69%	5.90%	5.74%

* Work done by Prof. C. Rasmussen of the Department of Anatomy, University of Minnesota.

About 100 cells from the ventral horn of the spinal cord (6 cc.) of experimental animals were projected and outlined on standard paper; 100 cells from normal animals were treated similarly, and the areas were cut out and weighed. This showed no significant difference in the size of the cells in either of the groups. Direct measurement of 50 nuclei from ventral horn cells of each animal showed no difference in the size of the nuclei. In the cerebellum, the Purkinje cells and the cerebral cortex and the larger pyramidal cells were compared in a general way. No difference was apparent.

COMMENT AND SUMMARY

Since the term fatigue is so often misused and since there seems to exist a great difference of opinion as to just what it means, let us first define what we understand by chronic fatigue. We do not have reference to fatigability which may appear as one of many symptoms of

organic disease nor do we have in mind acute fatigue which can be artificially produced in normal children and which is the inevitable result of certain prescribed amounts of work. What we have in mind in the term chronic fatigue is a symptom complex which may be primary, yet is often secondary, and in which the signs and symptoms of sub-efficiency are usually universal and in which more than one organ and more than one system are involved. The symptoms of fatigue may be psychic, physical or mental in character. These are varied, differing at times even in the same individual. In some children the psychic, in others the physical, may predominate. The course is slow and insidious. Our cases for study were selected on the basis of the first point and one or more of the remaining four points which follow:

1. The complaint must be of more than three months' duration.

2. The child must complain of feelings of fatigue.

3. There must be an actual decrease in the child's average mental achievement.

4. There must be an actual decrease in the child's average strength and endurance.

5. There must be an emotional unbalance.

In our study of the effect of undernutrition on activity, we showed that primary malnutrition due to partial inanition inevitably produces nervous irritability and increases the total activity.

We have now shown that forced exercise over a period of time produces a decrease in voluntary output, a loss of smaller gain in weight and a change in the animal's behavior.

The decreased output of work of chronically fatigued children and the nervous irritability of so-called hyperkinetic children are analogous to the pictures found in undernourished and overexercised rats.

In our nutritional clinic, we had occasion to watch the progress of apparently normal children. As a routine procedure, we inquired into their habits of living and their efficiency by means of questionnaires. The study disclosed that children with bad habits, especially those of eating, usually became irritable and restless and finally suffered a loss in weight. Their work in school fell off, and their physical capacity was lowered to such an extent that they applied for an excuse from gymnasium. In general we found that the malnourished child sooner or later becomes a nervous child and, finally, a tired child. And, vice versa, the fatigued child suffering from the effects of mental or physical overstrain in the end becomes malnourished and nervous. Of course the causes of fatigue, undernutrition and nervousness in the child are far more complex than in the animal. It is also more difficult to separate and localize cause and effect. We believe, however, that further clinical studies will fully bear

out our experimental evidence that nervousness, fatigue and malnutrition are not separate entities but syndromes of the same process of functional disorders.

CONCLUSIONS

1. Forced exercise in a limited space of time at a given rate of speed produces loss in weight or a decreased gain in weight as compared to the normal.

2. Bleeding of the feet is not the cause of loss in weight.

3. Forced exercise produces a decrease in voluntary activity.

4. Forced exercise results in a change in behavior as manifested by increased blinking, irritability and restlessness.

5. No pathologic changes could be found on either gross or microscopic examinations of extremely exhausted rats which died while exercising.

INTRAPERITONEAL TRANSFUSION OF BLOOD*

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Within recent years numerous articles have appeared concerning the value of intraperitoneal transfusion of blood. Certain reports indicate that red blood corpuscles find their way into the blood stream within a short time, often within a few minutes, when injected intraperitoneally. Others offer evidence that the fluid portion of the blood may be absorbed first and the corpuscles later. Most authors emphasize the comparatively good results of transfusion by this route and point out the ease, convenience and simplicity as compared with the direct method.

I wish to call attention to the fact that blood absorption from the peritoneal cavity is sometimes an uncertain process, occasionally being too slow to be of any therapeutic value. McKhann [1] already has noted the uncertainty of absorption and reported seven cases in which intraperitoneal transfusions had been used on infants. Necropsy was performed on five, and blood in varying amounts was found in the peritoneal cavity from thirty-six hours to eleven days following the intraperitoneal transfusion. This is illustrated also in the following cases.

CASE 1.—An infant, aged 18 days, was very ill with pneumonia and sepsis. An intravenous transfusion was followed in one half hour by an intraperitoneal transfusion. Four days later at necropsy one half of the injected blood was recovered in a fluid state from the peritoneal cavity.

CASE 2.—An athreptic infant, 3 months of age, four days after an intravenous transfusion developed otitis media which was followed by septicemia. Two intraperitoneal transfusions were given on successive days. At necropsy five days after the first intraperitoneal transfusion, it was estimated that practically all of the injected blood was recovered from the peritoneal cavity.

Certain sick infants have an impaired capacity to absorb blood from the peritoneal cavity. Usually such infants are the ones who need and who would benefit most by transfusion. Because of uncertain absorption by other routes, transfusions in the case of patients who are gravely ill should be given intravenously. Exposure of the vein is rarely necessary.

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* From the Department of Pediatrics, College of Medicine, State University of Iowa.

1. McKhann, Charles F.: Boston M. & S. J. **195**:1241 (Dec. 30) 1926.

ORIGIN AND FATE OF ISO-AGGLUTININS IN BLOOD FROM THE UMBILICAL CORD*

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The relative frequency with which iso-agglutinins and agglutinogens are found in the blood of the infant at birth and during the early days of life has been investigated frequently. Happ [1] found the blood group completely established at birth in 16.3 per cent of forty-nine cases, and McQuarrie [2] in 11 per cent of 180 cases. Other authors reported percentages varying from these to 78.7 per cent of 197 cases, the figure quoted by Jones.[3]

All investigators, with the exception of von Decastello and Sturli,[4] agreed that the agglutinogens appear earlier and occur in a larger proportion of cases than the iso-agglutinins. A change has never been demonstrated in a blood group which was completely established. Happ [1] and Unger,[5] however, pointed out apparent changes in group by the accession of iso-antibodies previously lacking, and Smith [6] reported two cases in which the apparent change was caused by the loss of iso-agglutinins present in the cord blood.

Iso-agglutinins which are present in cord blood are usually the same as those present in the blood of the mother.[7] Hirszfeld and Zborowski [8] suggested the passive transfer of such iso-agglutinins

* Submitted for publication, Oct. 20, 1928.

* From the Department of Pediatrics and the William Pepper Laboratory, School of Medicine, University of Pennsylvania.

1. Happ, W. M.: Appearance of Iso-Agglutinins in Infants and Children, J. Exper. Med. **31**:313, 1920.

2. McQuarrie, I.: Iso-Agglutination in New-Born Infants and Their Mothers, Bull. Johns Hopkins Hosp. **34**:51, 1923.

3. Jones, B. B.: Iso-Agglutinins in the Blood of the New-Born, Am. J. Dis. Child. **22**:586 (Dec.) 1921.

4. Von Decastello, A., and Sturli, A.: Ueber die Isoagglutinine im Serum gesunder und kranker Menschen, München. med. Wchnschr. **49**:1090, 1920.

5. Unger, L. J.: Precautions Necessary in the Selection of a Donor for Blood Transfusions, J. A. M. A. **76**:9 (Jan. 1) 1921.

6. Smith, C. H.: Iso-Agglutinins in the New-Born, Am. J. Dis. Child. **36**: 54 (July) 1928.

7. Debre, R., and Hamberger, M.: Grouppes sanguins du nourisson, Compt. rend. Soc. de biol. **94**:1196 (May 7) 1926.

8. Hirszfeld, L., and Zborowski, H.: Gruppenspezifische Beziehungen swischen Mutter und Frucht und elektive Durchlässigkeit der Placenta, Klin. Wchnschr. **4**: 1152 (June 11) 1925; Sur la perméabilité elective du placenta en rapport avec le groupe sanguin de la mère et du fetus, Compt. rend. Soc. de biol. **92**:1253 (March) 1925; Sur la symbiose serologique entre la mère et la foetus, ibid. **94**:205 (Jan. 29) 1926.

from the mother to the fetus through the placenta. Hara and Wakao [9] strengthened this hypothesis by noting the subsequent disappearance of iso-agglutinins found in the cord blood. Smith,[6] in a recent paper, offered data showing that blood serum obtained from the infant between birth and the tenth day of life frequently lacked the iso-agglutinins found in cord serum. In other cases the iso-agglutinins, though present, were diminished in titer.

Collon [10] opposed the theory of placental transmission. He found iso-agglutinins in the cord serum which were different from those of the mother. He maintained, therefore, that the fetus, as well as the infant, is fully capable of producing its own iso-agglutinins. Rech and Wohlisch [11] concurred in this opinion.

The following data were collected during an investigation of the relation of jaundice in new-born infants to the development of the blood group.[12] The figures are analyzed with reference to their bearing on the placental transmission of iso-agglutinins, on the ability of the fetus to produce its own iso-agglutinins and on the development of the blood group from birth to the twelfth day of life.

Tests to determine the presence of iso-agglutinins in infants were made on the first day of life with the use of cord serum. Cells used in tests for agglutinogens were collected directly from the infant.

If agglutinogens were present in the cells of the infant on the first day of life, the blood was reexamined between the third and seventh days, and again on the twelfth day. When they were absent on the first day, the blood was reexamined every second day until the twelfth day, or until they appeared, in which case their presence was checked on the twelfth day.

One test for the presence of iso-agglutinins was made on the infant's serum between the third and twelfth days of life. If negative results were obtained, another examination was made whenever possible (in 33 per cent of these cases).

TECHNIC

The technic used is a modification of that described by Jones.[3]

Serum obtained from cord blood which had remained in sterile test tubes at room temperature for an average of eleven hours was tested immediately for the presence of iso-agglutinins. Blood used in subsequent examinations of the infant's serum was obtained by venipuncture. The serum was removed after centrifugation

9. Hara, M., and Wakao, R.: Isohämoagglutination beim Kinde und in der Frauenmilch, Jahrb. f. Kinderh. **114**:313, 1926.

10. Collon, N. G.: Les isoagglutinines chez la mère et l'enfant, Compt. rend. Soc. de biol. **96**:144 (Jan. 21) 1927.

11. Rech, W., and Wohlisch, E.: Die gruppenspezifischen Eigenschaften des Blutes bei Neugeborenen und ihren Müttern, Ztschr. f. Biol. **84**:515, 1926.

12. Mitchell, J. McK.: The Rôle of Hemolysis in Jaundice of the New-Born Infant, Am. J. Dis. Child. **36**:486 (Sept.) 1928.

and was examined immediately. Serum used in tests on the blood of mothers was similarly obtained and handled.

By incision of the infant's heel, blood was collected in uniform amounts in a solution of 2 per cent sodium citrate in 1 cc. of 0.85 per cent sodium chloride, and used in tests for the presence of agglutinogens. Blood was obtained from the mother by venipuncture and collected in a similar solution.

The serum was tested against adult cells of known groups A and B, collected as described on every third day and kept on ice. Stock serums of groups O, A and B, kept on ice in sealed tubes, were tested against the cells of infant and mother. A control test of stock serums against stock cells was made at the time of each determination.

In ascertaining the presence or absence of iso-agglutinins, one drop of stock cells in approximately 5 per cent suspension was placed, with 4 drops of infant's serum of similar volume, on an ordinary glass slide. In the determination of agglutinogens, 2 drops of stock serum was used against 1 drop of infant's cells. The resultant combination of serum and cells was thoroughly mixed with a platinum wire and immediately examined under a microscope. After the mixture had stood for ten minutes at room temperature, a cover-slip was applied, and the slide was reexamined. The preparation was then incubated at 37 C. for thirty minutes and examined a third time.

TABLE 1.—*Terminology for Blood Groups*[13]

New Terminology	Jansky	Moss	Iso-agglutinins	Agglutinogens
O	I	IV	a and b	None
A	II	II	b	A
B	III	III	a	B
AB	IV	I	None	A and B

The strength of the reaction was estimated on the basis of whether it occurred immediately, at the end of ten minutes or only after incubation, and whether it was definite or weak.

RESULT OF TESTS

The new terminology for blood groups which is employed is found in table 1, together with that of the older Jansky and Moss groups.

Time of Development of the Blood Group.—In all, 902 examinations were made of the blood of 154 new-born infants and fifty-eight mothers to determine whether iso-agglutinins and agglutinogens were present. Of 120 infants whose cord serum and cells were both examined within twenty-four hours after birth, forty-eight, or 40 per cent (table 2), had their blood group completely formed; in twenty-three infants, agglutinogens alone and in twelve, iso-agglutinins alone were present. On the twelfth day of life, the blood group was found to be complete in sixty-seven, or 56 per cent, of 120 infants, and incomplete in 26 per cent.

13. Koeckert, H. L.: A Study of the Mechanism of Human Isohemagglutination, J. Immunol. **5**:529, 1920. Gichner, M. G.: A Biologic Mechanism of Human Isohemoagglutination, J. A. M. A. **79**:2143 (Dec. 23) 1922. New Designations for Blood Groups, editorial, J. A. M. A. **88**:1421 (April 30) 1927.

Iso-Agglutinins in Cord Serum Compared with Those in Infant's Serum.—Of 120 cases in which the cord serum was examined, iso-agglutinins were found to be present in 60. In forty-seven of the sixty cases the infant's serum was examined; in thirteen of them, more than once. Reexamination was made in fifty-two of the sixty cases in which iso-agglutinins were absent in the cord serum.

The most striking outcome of these reexaminations of the infant's blood was the fact that in ten cases in which iso-agglutinins originally were present in the cord serum, there was none to be found on one or more subsequent examinations (table 3). The supposition is that the iso-agglutinins which had been present in the cord blood were trans-

TABLE 2.—*Blood Groups at Birth and on the Twelfth Day*

	Birth		Twelfth Day	
	Number	Per Cent	Number	Per Cent
Group complete	48	40	67	56
Group incomplete	35	29	31	26
Group absent	37	31	22	18
Total	120		120	

TABLE 3.—*Comparison of Iso-Agglutinins in Cord Serum and Infant's Serum*

	Cord Number	Infant Number	Per Cent
Iso-agglutinins present	47	..	..
Iso-agglutinins lost	..	10	21
Iso-agglutinin titer decreased	..	7	15
Iso-agglutinin titer unchanged	..	23	49
Iso-agglutinin titer increased	..	7	15
Iso-agglutinins absent	52	.	..
Iso-agglutinins appearing for first time within twelve days	..	19	..

mitted by the mother through the placenta. Thus, in nine of the ten cases in which the iso-agglutinins disappeared, the blood group of the mother was the same as that of the infant as judged by its cells. In the tenth case, the blood group of the mother was O, that is, it contained iso-agglutinins *a* and *b*, while the cord serum contained iso-agglutinin *a;* the blood group of this infant, as judged by the cells, was B. In an additional seven cases, iso-agglutinins were still present in the serum of the infant, but they were noticeably weaker than in the cord serum. The blood group of the infant and of the mother was the same in all these cases.

In every instance, therefore, the iso-agglutinin which was present in cord serum and later was lost or weakened in titer could have come from the blood of the mother. It then would remain absent presumably until the infant elaborated his own iso-agglutinin. Support is added to this hypothesis by a case (table 8, K.E.) in which iso-agglutinins *a* and *b*

were present in the cord blood, *a* was missing on the eighth day, but reappeared on the thirteenth day. The mother's blood belonged to group O. In another case (table 8, L.A.) in which the mother's blood was in group A, iso-agglutinin *b*, present in the cord blood, was lost but reappeared on the ninth day. In a third case (table 8, S.W.), iso-

TABLE 4.—*Iso-Agglutinins in Cord Blood and Maternal Blood Which Are of Different Groups*

Infant	Group of Mother			Iso-agglutinins in Cord Blood	Final Group of Infant		
	Group	Cells	Serum		Serum	Cells	Group
1 (B. A.).....	O	O	a and b	a and b	a	B	B
2 (P. A.).....	O	O	a and b	a and b	a and b	AB	(?)
3 (M. G.).....	O	O	a and b	a	a	B	B
4 (M. A.).....	O	O	a and b	a	a	B	B
5 (H. Y.).....	O	O	a and b	a	a	B	B
6 (C. A.).....	O	O	a and b	b	b	A	A
7 (Z. U.).....	O	O	a and b	None	b	A	A
8 (O. V.).....	O	O	a and b	None	None	A	A(?)
9 (B. R.).....	O	O	a and b	None	None	AB	AB
10 (S. W.).....	A	A	b	b	a and b	O	O
11 (R. O.).....	A	A	b	None	None	AB	AB
12 (H. R.).....	B	B	a	a and b	a and b	O	O
13 (G. O.).....	B	B	a	a	None	AB	AB
14 (S. I.).....	B	B	a	None	None	A	A(?)
15 (W. I.).....	B	B	a	None	None	AB	AB
16 (T. A.).....	AB	AB	None	a and b	a and b	O	O

TABLE 5.—*Determination of Blood Group in Case B. A.**

Day of Life	Cells	Serum	Titer	Auto-agglutination
1	None	a and b	Immediate, weak Incubated, definite	
3	.....	a and b	Immediate, weak Incubated, weak	
6	None	a and b	a—Incubated, weak b—Incubated, definite	
8	None	b	Immediate, definite	
10	None	b	Immediate, definite	None
11	A	.....	Immediate, definite	
13	A	.....	Immediate, definite	

* Listed as first case in table 4: Full term negro baby, second child, delivery normal, birth weight of 2,730 Gm. regained on tenth day. Indirect van den Bergh test on third day, 12 units. Jaundice ++. Mild conjunctivitis. Gross abnormalties were not shown. Progress uneventful until discharge on fourteenth day.
Mother's group O; serum a and b.

agglutinin *b* in the cord serum was lost, but both *a* and *b* eventually appeared in the infant's serum. The mother's blood belonged in group A.

That the infant is actively elaborating his own iso-agglutinins during the first twelve days of life is verified by their presence at this time in nineteen of fifty-two cases in which they were absent in the cord serum. The seven cases which showed an increase in titer in the infant's serum as compared with the cord serum probably fall in a similar group.

Hirzfeld and Zborowski [8] stated that iso-agglutinins reach the blood stream of the infant most often when the mother and infant both belong to group O. This fact is borne out by tests in this series. Iso-agglutinins were present in the cord blood in eleven cases in which both the mother's and the infant's blood were in group O, but in only nine of twenty cases in which the blood of both belonged to group A or B.

Cases in which the Blood Group of the Mother and of the Infant Differed.—There was a total of fifty-eight cases in which the blood

TABLE 6.—*Determination of Blood Group in Case P. A.**

Day of Life	Cells	Serum	Titer
1	None	a and b	Incubated, definite
7	AB	.....	Incubated, definite
8	AB	.....	Incubated, definite
13	AB	a and b	Incubated, definite
14	AB	.....	Incubated, definite
15	.....	a and b	Incubated, definite
18	AB	.....	Incubated, definite

* Listed as second case in table 4: Full term, normal delivery, sixth child, white, birth weight 4,250 Gm. Fine tremors and nystagmus noted on day of birth. Lumbar puncture on second day gave bloody fluid; temperature, 102 F. On third day revealed purpuric spots and oozing from cord. Received 30 cc. of mother's blood intramuscularly. Jaundice ++. Sixth day, more purpuric spots; 30 cc. of mother's blood injected intramuscularly. Discharged on eighteenth day, weight, 3,785 Gm. Condition fair.
Mother's group O; serum a and b.

TABLE 7.—*Determination of Blood Group in Case G. O.**

Day of Life	Cells	Serum	Titer	Auto-agglutination and Autohemolysis
1	AB	a	Cells—Immediately definite Serum—Immediately weak Incubated, definite	None
3	AB	..	Immediate, definite	
4	AB	..	Immediate, definite	
5	AB	..	Immediate, definite	
6	AB	None	Immediate, definite	None
12	AB	..	Immediate, definite	

* Listed as case 13 in table 4: Full term, normal delivery, fourth child; birth weight, 2,960 Gm. No jaundice. Van den Bergh (indirect), on cord blood, 2.4; on sixth day, 3.5. Course uneventful. Discharged in good condition on thirteenth day; weight, 3,330 Gm.
Mother's group B; serum a.

group of the mother was determined and examination of the cord and infant's blood was complete. In thirty-two, the group of the mother and the infant was identical; in sixteen it differed, and in the remaining ten the infant's group could not be determined.

A more detailed analysis of the sixteen cases in which the groups of the mother and of the infant differed is important since it is the basis of proof that the fetus is able to elaborate its own iso-agglutinins, as maintained by Collon [10] and by Rech and Wohlisch [11] (table 4). Evidence of this fact appears in two cases. In one case (T.A.) the serum of the mother, whose blood belonged to group AB, did not contain iso-

agglutinins; both iso-agglutinins *a* and *b*, however, were present in the cord serum, and the infant's blood eventually belonged to group O. In the other case (H.R.), the serum of the mother, who was in group B, contained iso-agglutinin *a*, whereas the cord serum contained both iso-agglutinins *a* and *b* and the infant's blood eventually belonged to group O.

To appreciate the full significance of these observations, it must be realized that in only seven of fifty-eight cases was it possible for the cord serum to contain iso-agglutinins which were not present in the blood of the mother. In the remainder, the blood of the mother and that of the infant belonged to the same group; the mother's blood group was O, or the infant's group AB. In two of these seven the cord serum contained iso-agglutinins which could not have come from the mother.

The cord serum in eight of the remaining cases contained iso-agglutinins; this was explicable on the basis of transmission by the

TABLE 8.—*Cases with Apparent Change of Group*

Day of Life	Case 1 (K. E.)		Case 2 (L. A.)		Case 3 (S. W.)		Case 4 (W. A.)		Case 5 (G. A.)		Case 6 (S. N.)	
	Cells	Serum	Cells	Serum	Cells	Serum	Cells	Serum	Cells	Serum	Cells	Serum
1	None	a and b	None	b	None	b	None	a and b	A	None	B	None
2	.....	.....	None	.....	None	.....	None	.....	.....	.....	.....	.....
3	None	.....	.....	None	.....	.....	None	.....	.....	.....	AB	.....
4	None	.....	None	.....	.....	None	None	b	A	.....	.....	.....
5	.....	.....	.....	None	.....	.....	None	.....	.....	None	AB	None
6	None	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
8	.....	b	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
9	.....	.....	None	b	None	.....	None	.....	A	.....	.....	.....
10	None	.....	.....	.....	.....	a and b	.....	.....	.....	.....	.....	.....
11	.....	.....	None	.....	.....	.....	.....	.....	AB	.....	.....	.....
12	.....	.....	A	.....	None	.....	None	a and b	AB	None	AB	.....
13	None	a and b	A	.....	.....	.....	.....	.....	.....	.....	.....	.....
18	None	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
Group	Infant, O Mother, O		Infant, A Mother, A		Infant, O Mother, A		Infant, O Mother, ..		Infant, AB Mother, ..		Infant, AB Mother, ..	

mother despite the infant's eventual difference of group. This is, in fact, the only possible explanation of the observations in three cases (table 4, cases 1, 2 and 13). It is noteworthy that in all the cases showing these unusual conditions the final blood group of the mother and the infant differed.

Cases With Apparent Change of Group.—Five cases apparently changed group. A detailed analysis of the determinations made on various days (table 8) makes the cause of these apparent changes clear, and shows that they were not in any instance due to loss of iso-agglutinins save where their presence can be explained by transmission from the mother. Apparent change occurring in the cells is clearly due in each instance to the addition of receptors to complete group AB. If this group were more common, such instances doubtless would occur more frequently.

Cases of Premature or Stillborn Infants.—Of five cases in which the cord serum of premature infants (2,250 Gm. or less) was obtained,

iso-agglutinins were present in three and agglutinogens in two; the group was not complete in any case.

The cord serum of four of seven stillborn infants contained iso-agglutinins; unfortunately the blood group of the mother was not determined. In two of the infants lacking iso-agglutinins, fetal movements had not been felt for one month and one week, respectively, before delivery.

In one case a mother with hypertension and nephritis was delivered by section of a living fetus reckoned to be between 4½ and 5 months of age; the blood of the fetus contained agglutinogens A and B.

SUMMARY

The blood group was demonstrated to be formed completely at birth in 40 per cent of 120 new-born infants and incompletely in 29 per cent.

On the twelfth day of life, the blood group was completely formed in 56 per cent of the series and incompletely in 26 per cent.

Evidence indicating the placental transmission of iso-agglutinins is offered by the fact that in ten of forty-seven cases which disclosed them in the cord serum, the iso-agglutinins were lost completely and in seven their titer was diminished. In each case an identical iso-agglutinin was present in the blood of the mother. Strength is added to this hypothesis by cases in which the iso-agglutinins lost in this way eventually reappeared. That transmission most frequently occurs when mother and infant both belong to group O is suggested by the greater percentage of such cases containing iso-agglutinins at birth.

The ability of the fetus to elaborate its own iso-agglutinins is evidenced by the fact that in two cases of a possible seven, the cord serum contained iso-agglutinins not present in the serum of the mother.

Iso-agglutinins and agglutinogens are formed between birth and the twelfth day of life, as proved by 16 per cent additional cases in which the blood group was completely formed on the twelfth day, and by nineteen cases in which iso-agglutinins were absent in the cord blood but were present by the twelfth day.

Five cases have been presented in which there was an apparent change in the blood group. Detailed analysis showed that the change was due either to the loss of iso-agglutinins present in the cord serum, to which they were transmitted by the mother, or to the addition of iso-agglutinins or receptors to those present at birth. These changes were not due in any instance to the replacement of a factor once present in the blood of the infant.

Iso-agglutinins were demonstrated in the cord serum of four stillborn infants. Agglutinogens were present in the blood of a viable fetus of the fifth month.

THE BACTERIOLOGY OF DRY MILK

WITH PARTICULAR REFERENCE TO THAT MADE BY THE JUST PROCESS *

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A significant factor in extending the practical utility of dry milk for infant feeding is its high degree of bacterial purity and freedom from infectious organisms. Before reviewing the research which has established the fact that although properly prepared dry milk is not sterile in the strict bacteriologic sense, it contains relatively few harmless saprophytic species, it seems desirable to indicate briefly the factors contributing to the bacterial flora usually found in dry milk prepared by the two common processes. Since the application of heat by either method does not sterilize the milk completely, certain species which are present normally in the original fluid milk are found in the final product. In addition to these residual species, milk powder, as it is found on the market, may contain additional numbers and varieties of bacteria introduced by recontamination between the actual drying operation and the final packing. Even though these general conditions contribute to the bacterial flora of all desiccated milk, certain variations may be found in the kinds and numbers of organisms. These variations depend primarily on the method of desiccation employed, since each applies a different degree and amount of heat, rather than on the degree of recontamination. This is true, at least, of those establishments in which practical precautionary methods are used to protect the product.

In the spray method of drying, the milk is usually preheated to the usual pasteurizing temperature of from 142 to 145 F., at which it is kept for thirty minutes. The pasteurized milk is then condensed in a vacuum pan at a temperature rarely exceeding from 145 to 150 F., in some instances being as low as 123 F. After condensing, the milk may be sprayed, by any one of the several devices, into a heated chamber through which hot air circulates. The temperature of the dry air with which the milk comes in contact varies somewhat with the method employed, but a temperature of from 340 to 380 F. is not unusual. The milk, however, is not heated to this temperature, on account of the

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* From the research laboratories of The Dry Milk Company.

cooling effect caused by the rapid evaporation of the water. The temperature to which the particles of dry milk are actually heated before removal from the drying chamber probably does not exceed 180 F. in most instances, and in certain operations it may not exceed 150 F.

In the Just revolving cylinder process, cold milk (40 to 45 F.) is continuously supplied to the trough formed by two steam-heated steel cylinders which are tangent at their horizontal diameters and revolve inwardly in a contrary direction. During the brief interval in which the milk is held in the trough, it reaches the boiling point; at this temperature it is continually drawn between the cylinders into a thin film approximately 0.027 mm. in thickness. The speed at which the cylinders revolve is such that this thin film of milk is exposed for about two and a half seconds to a temperature accurately determined to vary between 250 and 258 F.

From the foregoing data, it is to be noted that the two principal methods of drying milk, which of necessity must utilize the same number of heat units for evaporating a given amount of water, employ, nevertheless, somewhat different principles of heat application and ratios of time to intensity of temperature. These relationships are particularly significant in interpreting the results of bacterial analyses of milk powders.

The greater part of the recorded data pertaining to the bacteriology of dry milk concerns the products made by the roller processes, although certain data are available concerning the products made by the spray process. The various studies have dealt with: the numbers and types of bacteria found in dry milk; the inability of certain species, particularly the tubercle bacillus, to survive the drying process; the degree of recontamination after desiccation, and the survival of the flora of the dry product during variable periods of storage. Hoffman [1] added cultures of the tubercle bacillus to milk and dried the infectious mixture by the double roller process. Guinea-pigs that were inoculated subcutaneously with the sediment obtained by centrifugating the reconstituted dry milk failed to develop tuberculosis. Bacteriologic examinations, by Grosso,[2] of dry milk prepared by the roller process revealed from 4,000 to 5,000 bacteria per gram, including such organisms as *Bacillus brevis, Bacillus subtilis, Streptococcus varians* and other common saprophytic forms. No pathogenic types were found. Kossowicz [3] found from forty-five to eighty bacteria per gram of powder taken directly from the drying cylinders, whereas that taken from the collecting boxes contained from 750 to 1,250 organisms per gram. This

1. Hoffman, W.: Arch. f. Hyg. **59**:216, 1906.
2. Grosso, G.: Ztschr. f. Fleisch-u. Milchhyg. **17**:312, 1907.
3. Kossowicz, A.: Ztschr. Landw. Versuchswesen in Osterreich **2**:719, 1908.

recontamination included micrococci, *Sarcinae*, streptococci, molds and yeast. After the powder was stored in hermetically sealed containers for two months, it showed only about 50 per cent of its original bacterial content, the decrease being due to the inability of certain species to survive the conditions of dry storage.

Klein [4] published a report of experiments in which tuberculous milk dried by the Eckenberg roller process was used. Guinea-pigs inoculated with the infected fluid milk showed definite tuberculous lesions after twenty-one days, whereas those inoculated with the dried product did not show these lesions on postmortem examination after the same period. Klein also performed other experiments with milk inoculated with *Bacillus coli, Bacillus typhosus,* the diphtheria bacillus, and a mixture of *Staphylococcus aureus* and *Bacillus prodigiosus.* All of these organisms were found to have been destroyed by the drying process described. In the experiments conducted by Carre [5] and by Martel,[6] milk that was heavily infected with virulent tubercle bacilli was dried by the Just roller process. Intraperitoneal injection and ingestion of the resulting powder did not produce tubercular lesions in guinea-pigs or monkeys.

Downs,[7] in an unpublished thesis, reported the presence of staphylococci, *Sarcinae,* members of the *Streptococcus lacticus* group and spore-bearing bacilli in practically all the samples of dried milk examined. His results showed that powders made by the spray process have a higher bacterial count than powders prepared by the roller process. Stocking [8] recorded about 20,000 bacteria per gram as the average content of more than 2,800 samples of powder prepared by the spray process; of these, 96 per cent contained less than 250,000 per gram.

Delepine [9] dried milk, heavily infected with the bovine tubercle bacillus, by the use of the heated cylinder and came to the conclusion that living tubercle bacilli might survive the process. Inoculation of guinea-pigs, however, showed that the course of the disease was much delayed by those organisms which had been subjected to the heat of the drying cylinders. Feeding with the dried tuberculous milk failed to produce any evidence of infection. Delepine's observations, which

4. Klein, quoted in Reports to the Local Government Board, n. s. 116, Food Reports, 1918, no. 24, p. 44.

5. Carre, H.: Soc. Cent. de Med. Vet., 1910, p. 556.

6. Martel, H.: Soc. Cent. de Med. Vet., 1910, p. 563

7. Downs, P. A.: Thesis, Cornell University Library, 1920.

8. Stocking, W. A.: Manual of Milk Products, New York, The Macmillan Company, 1917.

9. Delepine, S.: Reports to the Local Government Board, n. s. 97, Food Reports, 1914, no. 21.

contradict all published work of a similar character, are difficult to explain. In discussing the matter, he concluded that the maximum temperature reached by every part of the milk did not exceed 205 F., and that the duration of the exposure never exceeded three and three-tenths seconds. If these conclusions are correct, it is evident that his results were not obtained from the operation of a normally conducted Just process. Delepine also showed that a total count of more than from 265,000 to 588,000 bacteria per gram of fluid milk was reduced by the roller process to from 70 to 300 bacteria per gram of powder as it fell from the hot rollers, but that recontamination on subsequent handling might greatly increase these figures. The organisms found were staphylococci, a few streptococci, *Sarcinae*, sporulating bacilli, streptothrices and a few molds. His investigation of the spray process method of drying showed a higher number of bacteria per gram of powder than was found in the product prepared by the roller process; the counts ranged from 110,000 to 154,000 organisms per gram, and the flora included a moderate number of streptococci, many saprophytes, *Sarcinae*, a few Bacillus coli-like bacilli, large sporulating bacilli, streptothrices, yeast and molds. None of the forty-two samples of various powdered milks submitted to the Lister Institute [10] produced tuberculosis in guinea-pigs kept under observation for six weeks after inoculation. Thirty-six samples had counts of from no bacteria to 870 per gram; four samples contained between 1,000 and 2,278, and two contained 43,000 and 89,000 per gram.

Supplee and Ashbaugh [11] found that the number of bacteria in powder prepared by the roller process did not depend on the bacterial content of the original milk. Nine samples of milk containing from 1,520,000 to 345,000,000,000 bacteria per cubic centimeter gave powders which contained from 200 to 880 bacteria per gram. The montly average of daily bacterial counts in dry milk manufactured in routine production by the Just process ranged from 405 to 1,785 bacteria per gram; only three of the averages were above 1,000. Jephcott, Hunwicke and Ratcliffe [12] likewise reported a low bacterial content in dry milk prepared by the routine method of the roller process when proper provisions were taken to prevent recontamination. In the dry milk produced during one month, more than 90 per cent of the samples showed a count of less than fifty bacteria per cubic centimeter, while 6 per cent were completely sterile. Later, Hunwicke and Jephcott [13] inoculated milk with human

10. Reports to the Local Government Board, n. s. 116, Food Reports, 1918, no. 24, p. 122.

11. Supplee, G. C., and Ashbaugh, V. J.: J. Dairy Sc. **5**:216, 1922.

12. Jephcott, H.; Hunwicke, R. F., and Ratcliffe, N.: Proceedings of the World's Dairy Congress **2**:1265, 1924.

13. Hunwicke, R. F., and Jephcott, H.: J. Dairy Sc. **8**:206, 1925.

and bovine tubercle bacilli and dried it by the double cylinder process under normal operating conditions. Guinea-pigs inoculated intramuscularly with the reconstituted milk did not develop tuberculosis. These experimenters concluded that "the roller process of milk drying is capable of either destroying or rendering completely avirulent *Bacillus tuberculosis* of both human and bovine origin." These investigators also added other species of bacteria to milk and dried the mixture by the roller process. The results are shown in table 1.

Dick and Dick [14] recently examined two samples of powdered protein milk and found 88,000 and 80,000 bacteria per gram. A sample of powdered modified milk contained 19,000 bacteria per gram, and a sample of powdered whole milk contained a bacillus which spread too rapidly to make accurate counts possible. Three of these samples were found to contain 12,000, 30,000 and 10,000 green-producing strepto-

TABLE 1.—*The Destruction of Bacteria in Milk by the Roller Process, Reported by Hunwicke and Jephcott*

Type of Bacteria	Bacteria per Cubic Centimeter in Fluid Milk	Bacteria per Cubic Centimeter in Reconstituted Dry Milk
Bacillus coli	300,000,000	0
Bacillus cloacae	2,000,000,000	4
Capsulated, producing red pigment	320,000,000	0
Sarcinae lutea	1,000,000	0
Staphylococcus albus	510,000,000	0
Long chain streptococcus	10,000,000	0
Bacillus mycoides, spore-bearing	120,000,000	47,000
Bacillus subtilis, spore-bearing	2,000,000	50,000

cocci, respectively, per gram of powder, and a variety of spore-bearing bacilli, *Sarcinae,* staphylococci, gram-negative bacilli and lactic acid bacilli. In one sample of powdered protein milk these authors reported 700 hemolytic streptococci per gram. They concluded that "the presence of a variety of living bacteria, including streptococci, in preparations of powdered milk indicates that the methods of manufacture did not destroy the bacteria in the milk and that the bacteria remain viable in the powder." In a later report, Dick, Dick and Williams [15] recorded an epidemic of enteritis among infants which was shown to be caused by the Morgan dysentery bacillus. One is led to infer that feeding with dry milk was one of the contributing causes of the infection. The epidemic was brought to an abrupt end with the adoption of special prophylactic measures which included the substitution of boiled milk

14. Dick, G. F., and Dick, G. H.: Bacteriology of Dried Powdered Milk Preparations Used in Infant Feeding, Am. J. Dis. Child. **34**:1040 (Dec.) 1927.

15. Dick, G. F.; Dick, G. H., and Williams, J. F.: Etiology of Epidemic of Enteritis Associated with Mastoiditis in Infants, Am. J. Dis. Child. **35**:955 (June) 1928.

for the dry milk preparations, the boiling of all water and other precautions. It was not stated that boiled water was used for the preparation of the feedings of dry milk nor did it mention the process by which the milk powder was made.

The published experimental evidence on the whole establishes the paucity of micro-organisms in preparations of dry milk, particularly in those prepared by the Just process, and discloses the inability of many pathogens to survive the heat of the desiccating process. The recently reported presence of hemolytic streptococci and of inferential evidence that dry milk might have contributed to an epidemic of entertitis among infants seems, therefore, to indicate a bacterial character of milk powder not heretofore reported. The present investigation was undertaken to secure additional data similar to that previously reported; to determine the viability of certain organisms after subjection to the temperatures used in the Just roller process, and to make certain qualitative and quantitative bacteriologic comparisons between powders produced by the two methods that are in common use.

EXPERIMENTAL WORK

In order that representative and typical results might be obtained, the samples examined (unless otherwise noted) were obtained under the normal operating conditions prevailing in commercial factories using the Just double roller process, and during the production of a commercial product which is widely used for the feeding of infants. The first series of examinations were made with the twofold purpose of determining the number and general types of bacteria which survived the heat of the rolls, and the degree and quality of recontamination taking place from the time the dried powder was removed from the heated cylinders until it reached the final container. All samples were collected under approved aseptic conditions. The powder was reconstituted with sterile water to the basis of fluid milk, and suitable dilutions were plated with nutrient agar containing 0.8 per cent sodium chloride and 5 per cent sterile defibrinated horse blood. Triplicate plates were incubated at 37 C. for forty-eight hours. Total counts of bacteria and hemolyzing colonies were made. All types of hemolyzing colonies with the exception of spreaders were obtained and examined under the microscope. Those forms for which a morphologic diagnosis was doubtful were transferred into infusion broth for the subsequent production of subcultures and further observation. A differential count of alpha and beta hemolyzing types was not attempted. Table 2 shows the results obtained from samples taken directly from the drying cylinders and after the powder had been further prepared for final packing. Table 3 shows the results obtained from the same product made at another factory. In this series, however, samples were not obtained directly

TABLE 2.—*Bacterial Content of Milk Direct from Drying Cylinder and Ready for Packing at Factory "B"* *

Direct From Drying Cylinders				At Time of Final Packing			
Sample	Total Count	Count of Hemolyzing Colonies	Count of Hemolyzing Colonies Less Than 2 Mm. in Diameter	Sample	Total Count	Count of Hemolyzing Colonies	Count of Hemolyzing Colonies Less Than 2 Mm. in Diameter
1 R	80	30	..	1 B	80	60	..
2 R	130	90	..	2 B	180	140	..
3 R	6	0	0	3 B	700	460	..
4 R	40	34	..	4 B	120	0	0
5 R	130	35	15	5 B	340	55	15
6 R	75	25	7	6 B	105	15	7
7 R	55	20	0	7 B	155	30	7
8 R	280	45	25	8 B	220	7	7
9 R	115	20	20	9 B	140	20	7
10 R	100	80	6	10 B	180	60	20
11 R	100	40	20	11 B	100	14	6
12 R	60	35	6	12 B	540	260	200
13 R	65	20	6	13 B	180	34	0
14 R	80	65	14	14 B	135	95	25
15 R	45	40	20	15 B	225	155	15
16 R	75	65	6	16 B	55	25	0
17 R	40	0	0	17 B	155	115	20
18 B	100	75	20	18 B	220	45	6
19 R	300	200	20	19 B	600	350	40
20 R	800	550	0	20 B	650	250	40
Average....	133	73	11		234	109	24

* Thirty additional samples from factory "B" were examined in the same manner, but since they were not comparable in the display of bacterial differences immediately after drying and before packing, they were not included in the table.

TABLE 3.—*Bacterial Content of Dry Milk from Factory "C"*

Sample	Total Count	Count of Hemolyzing Colonies	Count of Hemolyzing Colonies Less Than 2 Mm. in Diameter
1 C	480	0	0
2 C	600	73	..
3 C	380	0	0
4 C	560	53	..
5 C	600	26	..
6 C	480	20	..
7 C	920	120	..
8 C	520	80	0
9 C	420	140	0
10 C	360	180	0
11 C	1,260	7	7
12 C	325	15	7
13 C	320	20	20
14 C	360	0	0
15 C	300	5	0
16 C	580	0	0
17 C	540	15	7
18 C	250	0	0
19 C	200	0	0
20 C	380	60	6
21 C	1,300	360	0
22 C	600	130	20
23 C	1,200	80	40
24 C	1,100	540	480
25 C	285	20	20
26 C	225	40	15
27 C	765	6	6
28 C	355	55	15
29 C	955	25	6
30 C	425	20	0
31 C	475	245	125
Average	564	75	29

from the drying cylinders, and the results recorded are those from composite samples taken daily from the commercial production.

These two series of examinations disclose that the average total count of bacteria was 264 per gram in the product from one factory and 564 per gram in that from the other. A comparison of the results which were obtained from samples taken directly from the drying cylinders and those from the final product ready for packing showed that in all instances there is a slight increase in bacterial content after the product leaves the drying cylinders. While this average increase is about 100 per cent, the sanitary significance of this ratio is practically nil because of the low initial count of bacteria. While it is recognized that the hemolytic properties themselves have little if any differentiating value, it is significant that the count of the hemolytic colonies is increased at about the same rate as the total count of bacteria. This is interpreted as showing that the recontaminating organisms in these samples of dried

TABLE 4.—*Average Number of Bacteria Per Gram in Milk Powder Prepared by the Just Process, as Revealed in Samples Taken Daily from Commercial Production for Seven Years*

Year	Average Number per Gram for Year	Maximum Monthly Average, Number per Gram	Minimum Monthly Average, Number per Gram
1921	780	1,135	440
1922	330	910	380
1923	564	1,025	302
1924	422	961	161
1925	472	687	209
1926	510	856	292
1927	707	1,482	244

milk are not substantially different from those in the normal fluid milk which survived the heat of the desiccating process.

In order that the colonies of suspicious appearance might be further differentiated, a total of 267 colonies, including 160 which were representative of all the hemolytic types found, were taken from the different samples and examined morphologically. Sixty-six per cent of the hemolyzing colonies were definitely classed as rods, 25 per cent as staphylococci and 9 per cent as micrococci. No streptococci were found in any of the samples. To show that the milk powder made by the Just process primarily for infant feeding has a uniformly low bacterial content as shown by the foregoing analyses (tables 2 and 3), table 4 includes results from daily analyses of samples of the commercial production for a period of more than seven years, plated on nutrient agar incubated at 37 C. for forty-eight hours.

A recent report by Dick and Dick [15] indicating the presence of hemolytic and green-producing streptococci in milk powder of undesignated origin made it advisable to determine by direct experimentation whether such types of bacteria can survive the Just process conducted

under the usual operating conditions. For this work, the hemolyzing *Streptococci epidemicus, asalignus* and *mastiditis* were used; also a green-producing streptococcus, enterococcus 1082 described by Orcutt,[16] and a culture of the Morgan dysentery bacillus. Frequently subcultures of all these strains were made in dextrose broth, infusion broth and blood agar in order to insure healthy and viable cultures. Finally, appropriate quantities of cultures made from infusion broth, twenty-four hours old, were mixed with suitable amounts of milk which previously had been heated to destroy all bacteria with the possible exception of the resistant spore formers. Plate cultures of the inoculated fluid milk showed the presence of the added organisms in numbers varying from 2,000,000 to 89,000,000 per cubic centimeter. Arrangements were made to control carefully the operation of a Just milk drying machine in order that the usual conditions might be maintained throughout the period required to desiccate about 80 pounds (36.3 Kg.) of each of the five inoculated milks. During the course of the drying operation, samples of the dry milk film were obtained under aseptic conditions immediately after removal from the surface of the drying cylinders. From two to three samples were obtained from each lot of milk. Plate cultures of the samples of powder obtained from the inoculated milk were made on blood agar within two days after drying. Careful examination of the incubated plates failed to reveal any of the particular species introduced into the milk before desiccation. From these results, it may be concluded that streptococci, hemolytic and green-producing, and the Morgan dysentery bacillus are killed by the heat of the Just milk drying process, a result which is entirely logical in view of the thermal death points of these organisms and the temperatures known to prevail during the desiccation of milk by this method.

This report would not be complete without certain data obtained from the bacteriologic examination of representative samples of milk powder made by one of the well known spray methods. Eight samples of the milk powder in question were purchased in the open market of four different states. The samples were reconstituted with sterile water and plate cultures were made in proper dilution on blood agar as previously described. The results which are shown in table 5 disclose that the total counts of bacteria and the counts of hemolytic colonies are uniformly much higher than those obtained from dry milk made by the Just process. Of fifty hemolytic colonies representing all such types found in the eight different samples, 66 per cent were found to be rods, 22 per cent staphylococci and 12 per cent micrococci. These relationships are remarkably similar to those found on examination of the hemolytic colonies derived from the milk powder produced by the

16. Orcutt, M. L.: J. Bact. **11**:29, 1926.

Just process. It is believed that these observations clearly indicate a fairly constant quota of heat-resisting hemolyzing types of bacteria normally present as part of the natural fluid milk flora. The presence of hemolyzing or green-producing streptococci was not definitely shown in any of these samples.

From the available literature and from the foregoing experimental evidence, it is to be noted that many saprophytes and the following pathogens have been shown to be destroyed by the Just process of drying milk: *B. tuberculosis; B. typhosus;* diphtheria bacillus; *S. aureus; S. epidemicus; S. mastiditis;* the Morgan dysentery bacillus, and the green-producing enterococcus. The presence of these organisms in dry milk prepared by this process is highly improbable, therefore, unless recontamination of a most unusual and improbable character takes place. The presence of pathogenic hemolytic streptococci in milk

TABLE 5.—*Bacterial Content of Powdered Milk Produced by the Spray Process*

Sample	Total Count	Count of Hemolyzing Colonies	Count of Hemolyzing Colonies Less Than 2 Mm. in Diameter
1	175,000	105,000	.....
2	27,000	13,000	.....
3	26,000	15,000	.....
4	95,000	26,000	.....
5	171,000	170,000	170,000
6	42,000	32,000	32,000
7	47,000	40,000	40,000
8	24,000	13,000	13,000
Average	75,800	51,700	

powder, irrespective of the method of manufacture, is to be accepted as a probability only after careful and thorough consideration of the difficulties of morphologic, cultural and pathogenic identification. Attention has been directed to this fact by Brown,[17] Davis,[18] Frost and Bachman,[19] and more recently by Frobisher and Denny.[20]

SUMMARY

1. The dry milk made by the Just roller process rarely has a bacterial content of more than 1,000 per gram.

2. A slight increase in the bacterial content may take place from the time the dry milk leaves the drying cylinders until it is packed. This degree of recontamination was found to be insignificant under the conditions reported in this paper.

17. Brown, J. H.: Monographs of the Rockefeller Institute for Medical Research, 1919, no. 9.

18. Davis, D. J.: J. Infect. Dis. **19**:236, 1916.

19. Frost, W. D., and Bachman, F. M.: Am. J. Pub. Health **13**:300, 1923.

20. Frobisher, M., and Denny, E. R.: J. Bact. **16**:109, 1928.

3. Hemolyzing bacteria, including rods, staphylococci and micrococci, many of which are shown to be survivors of the natural fluid milk flora, were found in approximately the same proportions in the milk powders made by the Just and by the spray processes. Hemolytic streptococci or green-producing streptococci were not found in the samples of powder made by either process.

4. The total bacterial count and the total count of hemolyzing colonies were found to be much higher in the milk powder prepared by the spray process than in that made by the Just process.

5. Hemolyzing streptococci, including *S. epidemicus,* enterococcus, a green-producing streptococcus, and the Morgan dysentery bacillus, all were destroyed by the Just milk drying process.

PAROXYSMAL HEMOGLOBINURIA *

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Paroxysmal hemoglobinuria is usually defined as a syndrome or condition, presumably caused by a syphilitic infection and manifesting itself by recurring paroxysms of hemoglobinuria and by characteristic constitutional symptoms. The blood of patients who suffer from this condition is presumed to contain, in latent form, a specific hemolysin which becomes active when the blood is chilled and which produces the paroxysms. On account of the part played by cold, the condition has been given such names as kälthamoglobinurie, hemoglobinuria a frigore and chilling hemoglobinuria.

The condition may occur at any age, but it is rarely observed in patients more than 50 years of age. It is as common in children as in adults. The majority of the patients are male.

Strictly speaking, the condition should not be described as paroxysmal. The attacks or crises can always occur under well defined conditions or can be induced artificially by similar conditions.

In general, hemolysis of varying degrees may follow a great number of pathologic conditions; it may result from physical causes or from the use of chemical or other drugs which penetrate the red blood corpuscles and disorganize them; it may also be a biologic effect due to the toxins arising from certain infections such as syphilis, malaria and recurring fever.

The amount of hemoglobinemia which follows the liberation of hemoglobin in the blood by such a lysis is not ordinarily more than can be managed easily by the liver; however, when the amount of free hemoglobin in the blood serum exceeds the power of the liver to cope with it, there is usually hemoglobinuria. Ponfick [1] and Stadelmann [2] each showed independently that this does not occur until the amount of free hemoglobin reaches one sixtieth of the total hemoglobin content of the body, and that a destruction of the red corpuscles may take place almost to the equivalent of this content without the appearance of hemoglobinuria. Clinically, a hemoglobinuria is always preceded by a hemoglobinemia which, however, may be of brief duration, as in the condition under discussion when the hemoglobinuria resembles a paroxysm.

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* Submitted for publication, Dec. 4, 1928.

1. Ponfick, E.: Ueber Hämoglobinemia und ihre Folgen, Berlin, 1883.

2. Stadelmann: Ueber die Folgen Subcutaner und intraperitonealer Hämoglobininjectionen, Arch. f. exper. Path. u. Pharmakol. **27**:93, 1890.

HISTORY OF PAROXYSMAL HEMOGLOBINURIA

Although the condition now known as paroxysmal hemoglobinuria was noted in a case observed by Stewart [3] at Archangel in 1794, and mentioned by Rayer in his "Treatise on Diseases of the Kidneys" in 1841, it was Dressler,[4] in 1854, in his monograph on "Intermittent Albuminuria and Chromaturia" who first gave a satisfactory clinical account of the condition. Dressler showed that the urine contained a dark red amorphous pigment without red blood corpuscles. Hassall,[5] in 1865, recognized that the pigment was hemoglobin and that the disease occurred almost exclusively during cold weather. The name paroxysmal hemoglobinuria was suggested first by Secchi [6] in 1868. Ringer,[7] in 1868, remarked that not only cold but other causes could give rise to crises of hemoglobinuria; Greenhow [8] thought that the condition was associated with malaria. Fleischer,[9] Strubing [10] and, later, Eason [11] upheld the view that the paroxysms or crises of hemoglobinuria could be brought on by great exertion independently of cold. Murri,[12] in 1880, was one of the first to publish the results of a systematic study of paroxysmal hemoglobinuria, and was one of the earliest also to associate the disease with syphilis. Chvostek,[13] in 1894, published an elaborate review of the literature and reported several cases which he personally had observed.

Although crises or paroxysms of hemoglobinuria undoubtedly may occur during the course of malaria, recurrent fever and other conditions, it does not appear that these crises are strictly identical with the crises of hemoglobinuria brought about by exposure to cold. The malarial attacks and similar conditions may be associated with anaphylactic shock or colloidoclasia but seem to differ from the hemoglobinuria due to chilling both in the characteristic constitutional

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3. Stewart, cited by Macalister: Quart. J. Med. **2**:368, 1908-1909.

4. Dressler, cited by Macalister.

5. Hassall, A.: On Intermittent or Winter Hematuria, Lancet **2**:368, 1865.

6. Secchi, cited by Macalister.

7. Ringer, cited by Macalister.

8. Greenhow, E.: Four Cases of Intermittent or Paroxysmal Hemoglobinuria, Tr. Clin. Soc. London **1**:40, 1868.

9. Fleischer: Ueber eine neue Form von Hämoglobinurie, Berl. klin. Wchnschr. **18**:691, 1881.

10. Strubing, P.: Paroxysmale Hämoglobinurie, Deutsche med. Wchnschr. **8**:1, 1882.

11. Eason, J.: Paroxysmal Hemoglobinuria, J. Path. & Bact. **11**:203, 1906.

12. Murri, A.: Della emoglobinuria da freddo, Bologna, 1880; Emoglobinuria e sifilide, Riv. clin. di Bologna **5**:321, 1885.

13. Chvostek, F.: Ueber das Wesen der paroxysmalen Hämoglobinurie, Leipzig, 1894.

symptoms and especially in the properties of the serum, which is both autolytic and isolytic in cases of hemoglobinuria. I am not aware that any investigation of malarial serum has been made in this direction.

The conception of paroxysmal hemoglobinuria following chilling of the blood as a reaction which follows the Ehrlich theory of the complement-antibody-cell combination was brought into especial prominence by the observations and studies of Donath and Landsteiner [14] in 1904. These investigators showed that if the serum of a patient with paroxysmal hemoglobinuria was mixed with his own washed red blood corpuscles in suitable proportion and was kept at 0 C. for half an hour, hemolysis occurred when the mixture was then heated to 37 C. for three hours in an incubator. The same phenomenon occurred when the serum of the patient was similarly treated with normal blood corpuscles from other persons. The serum from such persons, however, would not hemolyze the corpuscles of the patient when submitted to the same technic. It appears that the serum of a patient with paroxysmal hemoglobinuria contains a special amboceptor which becomes fixed to the corpuscles at a low temperature, in the presence of a complement, an autohemolysin which becomes active only when the blood is refrigerated.

Although Ehrlich, in 1885, had shown that when the ligatured finger of a hemoglobinuric patient was immersed in ice cold water, intense hemolysis occurred below the ligature in the finger, it was the studies of Donath and Landsteiner which gave the phenomenon a precise significance.

The investigations of Donath and Landsteiner were made in vitro, but they found that in patients with paroxysmal hemoglobinuria, such attacks could be induced at will by artificially exposing one of the extremities of the patient to a chilling temperature. The same clinical symptoms—chill, fever with or without abdominal pain, and the passing of dark red urine containing hemoglobin and albumin, without red corpuscles—were brought on when the patients were exposed to a cold, damp atmosphere; hence the subsequent universal use of the term "chilling hemoglobinuria."

REPORT OF CASE

Before entering into a general discussion of the subject, I wish to report a case of paroxysmal hemoglobinuria recently observed which occurred in a child as the result of chilling. As the fairly comprehensive literature shows, the subject is peculiarly fascinating, especially on etiologic grounds. The American literature on the subject is some-

14. Donath, J., and Landsteiner, K.: Ueber paroxysmale Hämoglobinurie, Ztschr. f. klin. Med. **58**:173, 1905.

what meager. Only a few of the published reports contain complete laboratory observations; and none contains data for a period including continuous attacks and intervals.

Case History.—A boy, white, American, aged 5 years, was born at full term. Breech presentation occurred, with version. The infant was not cyanotic and weighed at birth 5 pounds (2.3 Kg.). He was breast fed for twelve months and nursed well. Cereal was added to the diet at 6 months of age, and vegetables at 7 months; orange juice was given but cod liver oil was not included in the diet. At the age of 3½ months, the infant weighed 18 pounds (8.2 Kg.), but after the first year he did not continue to gain normally in weight. The first teeth erupted when the child was 6 months old. After the age of 1 year the child began to show signs of weakness without any apparent cause; he commenced to walk at 14 months of age, but fell often until he was 2½ years of age.

The child was bright and began to talk early. He was never especially active and was subject to frequent colds. At 2 years of age, he had whooping cough, which lasted all summer and resulted in the loss of considerable weight. At about the age of 3 years, the child was exposed to scarlet fever. He had a temperature of 103 F., and a red throat, but did not show any other symptoms. After two days, he recovered.

The mother was 27 years of age and was healthy. This was her only child. The history did not include miscarriages or familial antecedents of consequence. The father who was 30 years old was anemic; his color was purplish. He had a familial history of anemia; his father died of pernicious anemia at the age of 60 years; his mother was still alive and well.

Present Illness.—The patient was called to my attention by the mother on account of his passing dark red urine, with abdominal pain, chills and fever. The condition occurred periodically after exposure to cold air or a chill, moist atmosphere. The last attack occurred about two weeks before this report was submitted. The mother associated the first appearance of the condition with the child's exposure to scarlet fever; when she took him out on a damp day, he suddenly complained of severe abdominal pain and chills. On returning home he was listless and tired and asked to be put to bed. The chill subsided but was followed by fever. A half hour after the appearance of the fever, the child passed a large amount of dark red urine which was almost the color of coffee. After returning to bed he soon felt well enough to sit up and eat. The next day he was up and seemed normal, although he was weak and somewhat pale. One week later, after having been taken out on a chilly day, he had a similar attack. The family physician advised rest, and the child was kept in bed for two weeks. As the mother noticed that the attacks followed exposure to cold, the patient was not taken out in chilly weather. The attacks became less frequent but still followed any exposure to cold or dampness. The child frequently got cold clammy spells. He continued to be listless and refused to play.

Examination.—The patient was well developed physically and mentally. He was rather tall for his age and weighed 41 pounds (18.6 Kg.). The skin was clear; he did not disclose a rash or excessive fat; the tissue resistance was firm. The head and neck were normal; adenopathy was not present. The heart, lungs and bone development of the thorax were normal. The abdomen did not show tenderness or rigidity. The liver was found one fingerbreadth below the costal margin. The spleen was not palpable. The reflexes were normal. The only genital anomaly was a tight long foreskin.

Laboratory Data.—A chemical examination of the blood made on July 15, 1927, yielded practically normal percentages as shown in table 1. The Wassermann reaction of the blood as well as the Kahn reaction obtained from the child was 4+; the results of tests on the mother and father were negative. Two weeks later, the child again gave a 4+ Wassermann reaction. The Wassermann reactions on the spinal fluid obtained at the same time from the parents were negative. A test for fragility of the red blood cells which was made, using the Giffin and Sanford technic, gave 49-39. The results, which were not obtained during the attack, were rather low at the beginning of the test. The van den Bergh test, both direct and indirect, gave slightly positive results. The Donath and Landsteiner chilling test of the blood, using the serum of the patient mixed with his own blood corpuscles, gave results shown in table 2.

The history and observations suggested that the case was one of so-called paroxysmal hemoglobinuria. The mother was advised not to expose the child to cold and requested to report at once if another attack occurred. The patient was

TABLE 1.—*Content of the Blood Substance*

Substance	Mg. per 100 Cc.
Nonprotein nitrogen	49.0
Urea	5.8
Urea nitrogen	27.0
Uric acid	2.8
Creatinine	1.4
Calcium	14.0

TABLE 2.—*Results of the Chilling Test of the Blood by the Donath and Landsteiner Method*

Initial Temperature	Length of Time, Minutes	Incubation Temperature	Length of Time, Minutes	Extent of Hemolysis
0 C.	5	37 C.	30	Partial
0 C.	15	37 C.	30	Partial
0 C.	30	37 C.	30	Complete
0 C.	90	37 C.	30	Incomplete

put on antisyphiltic treatment in September, 1927. Six treatments with sulpharsphenamine in doses of from 0.1 to 0.2 Gm. were given, at intervals of one week. Ammoniated mercury was given in half-grain doses three times a day. No ill effects followed this treatment.

On Feb. 15, 1928, the patient was brought to my office for examination during another attack of hemoglobinuria. The mother stated that after the initial chills the temperature reached 103 F., and that half an hour later the child passed dark coffe-colored urine. The laboratory examination of a specimen of this urine showed: specific gravity, 1.038; albumin, 2+; hemoglobin, 4+; a few hyaline casts. The urine did not contain red blood corpuscles and did not show sugar or pus. Spectroscopic examination showed the absorption bands for methemoglobin and oxyhemoglobin.

A specimen of blood taken immediately after the beginning of the attack showed: red blood cells, 2,500,000; white blood cells, 11,000; hemoglobin, 50 per cent; lymphocytes, 45; polymorphonuclears, 50; mononuclears, 5; eosinophils, 2.5; basophils, 2; nucleated red cells, none, and slight poikilocytosis. The fragility test at this time gave 51 and 40 per cent. The coagulation time was one and a half and two minutes.

A Donath and Landsteiner chilling test made on the serum of the patient, mixed with his own blood corpuscles, gave the results shown in table 3.

On February 17, another examination of the blood showed an increase of 1,060,000 red blood cells and 15 per cent hemoglobin with a coagulation time of fifteen minutes. The urine was normal except for a trace of albumin.

The results of Donath and Landsteiner chilling test for blood, using the patient's serum and normal blood corpuscles, are given in table 4.

Some hemolysis was obtained after twenty-four hours in ice and following exposure to 37 C. The direct van den Bergh test gave slightly positive results; the indirect, decidedly positive and immediate results.

On February 19, the fourth day following the attack, the patient was seen again; he was pale but otherwise normal. An examination of the urine showed a few hyaline casts and a few red blood cells; hemoglobin, however, was not found.

The chilling test with the patient's serum and his own blood cells, and also with cells from other persons, gave practically the same results as the two preceding tests. The van den Bergh test, both direct and indirect, gave negative results.

TABLE 3.—*Chilling Test of the Blood by the Donath and Landsteiner Method*

Initial Temperature	Length of Time, Minutes	Incubation Temperature	Length of Time, Minutes	Extent of Hemolysis
0 C.	5	37 C.	30	Complete
0 C.	25	37 C.	30	Complete
0 C.	45	37 C.	30	Incomplete

TABLE 4.—*Chilling Test of the Blood by the Donath and Landsteiner Method*

Initial Temperature	Length of Time, Minutes	Incubation Temperature	Length of Time, Minutes	Extent of Hemolysis
0 C.	5	37 C.	30	None
0 C.	10	37 C.	30	Partial
0 C.	25	37 C.	30	Partial
0 C.	60	37 C.	30	None
0 C.	90	37 C.	30	Beginning

On February 20, the patient suffered another typical attack of hemoglobinuria following exposure in a chilly bath tub. The mother stated that a chill came on five minutes after immersion in the tub. The patient was pale and suffered severe abdominal pain, without abdominal tenderness. Following the chill the temperature rose to 103 F. One hour later, in my office, urine of a dark red wine color was passed, containing a trace of albumin and a slight trace of sugar. Spectroscopic examination gave absorption bands for metahemoglobin and oxyhemoglobin. The throat was red at that time; otherwise, a physical examination gave normal results.

The examination of the blood again showed diminution of red cells, hemoglobin and coagulation time. The globular fragility was 56 and 43. The chilling test gave the same results as before with the patient's own blood cells and with normal cells. The van den Bergh test, both direct and indirect, gave strongly positive results.

On February 21, the patient felt and looked better but was slightly pale. The temperature was 101 F., and the throat was still red. Examination of a specimen of urine showed a trace of albumin and a trace of hemoglobin. Examination of the blood showed a slight improvement in the number of red cells and in the amount of hemoglobin. The globular fragility was 48 and 38.

The child was kept in bed on account of the inflamed throat and recovered fully in three days. Following this attack the mother was again advised to avoid exposing the patient to cold; the wearing of heavy woolen stockings and underwear was also advised.

On April 2, the patient was examined and was found to be well; he had gained 4 pounds (1.8 Kg.) in six weeks. Antisyphilitic treatment was kept up every other day as before with iron citrate in doses of 5 grains (0.32 Gm.) three times a day.

The laboratory observations on April 2 showed that the urine was normal except for occasional hyaline casts. The blood count was normal, and the globular fragility was 46 and 37, or normal. The chilling test with the patient's serum and his own corpuscles still showed complete hemolysis after twenty-five minutes; the coagulation time was twelve minutes. At this date the Wassermann test for the patient's blood was 4+; the Wassermann test of the mother's blood tested twice was negative.

On April 7, the patient had another severe attack of hemoglobinuria, without marked change in the blood count. The chilling test gave the same results as that on February 15.

In June, a specimen of the patient's blood gave a Wassermann reaction of 4+; the Kahn test was also 4+. The Wassermann reaction of the mother's blood

TABLE 5.—*Changes in Red Blood Corpuscles in Paroxysmal Hemoglobinuria*

Time	Date	Red Blood Cells	Hemoglobin, per Cent
During attack	Feb. 15	2,500,000	50
Following attack	Feb. 17	3,560,000	65
Following attack	Feb. 19	3,800,000	..
During attack	Feb. 20	2,800,000	45
Following attack	Feb. 21	3,200,000	50
During interval between attacks	April 2	4,500,000	..
During attack	April 7	3,200,000	60

examined twice in the hospital was 3+. The father was not available for a blood test.

The patient's treatment was continued as before except that it was interrupted from June 20 to July 14. Then another typical attack of hemoglobinuria occurred following a cold bath. It should be stated that the patient's blood examined before, during and after attacks did not show any evidence of malaria. Nucleated red cells were not seen at any time. A slight poikilocytosis was noted. A fall in arterial pressure occurred at the period of attacks; diminution of blood platelets was observed between attacks.

DISCUSSION OF THE LABORATORY DATA

Changes in Blood.—The data in table 5 concerning the red blood corpuscles were obtained. These figures show that during an attack there is a rapid destruction of the red blood corpuscles with a rapid recovery in the number of corpuscles and the amount of hemoglobin content following the cessation of the attack. In the interval between attacks the number of red blood corpuscles is about normal. In several cases recorded in the literature in which attacks occurred in rapid succession, a state of anemia persisted. The changes in red blood corpuscles usually coincided with

those in the case described in this paper. In the case recorded by Macalister,[15] the corpuscles, during an attack, numbered 3,200,000; the following morning, 3,600,000; three days later, 3,900,000; and six months later, without any paroxysm in the interval, 4,500,000. The figures of Kobler and Overmeyer[16] give a count of 3,589,000, hemoglobin 90 per cent before the attack; 2,890,000, hemoglobin 85 per cent during the attack; and 3,810,000, hemoglobin 80 per cent following the attack.

During a severe induced attack in one case, Montagnani[17] found the red corpuscles as few as 1,800,000 and the hemoglobin 28 per cent. The new young corpuscles usually are deficient in hemoglobin.

White Blood Corpuscles.—Data concerning the white blood cells during, following and between attacks are summed up in table 6. The results show that there is a moderate leukocytosis during the crisis of the disease. The neutrophils are increased. The data generally

TABLE 6.—*Changes in White Blood Cells in Paroxysmal Hemoglobinuria*

Date	Leukocytes	Lymphocytes, per Cent	Polymorphonuclears, per Cent	Mononuclears, per Cent	Eosinophils, per Cent	Basophils, per Cent
Feb. 15 (attack)	11,000	45	50	5.0	2.5	2.0
Feb. 17	9,000	40	52	1.0	3.0	2.0
Feb. 19	9,000	A differential count was not made				
Feb. 20 (attack)	18,000	32	62	1.0	3.0	2.0
Feb. 21	12,000	A differential count was not made				
April 2 (interval between attacks)	7,000	A differential count was not made				
April 7 (attack)	11,000	A differential count was not made				

agree with those of other investigators in those instances in which examinations on the blood have been made. The leukocytosis recedes as the attack subsides. In the presence of an activated amboceptor leukocytes apparently are stimulated into greater activity.

Urinary Data.—The most significant clinical observation in paroxysmal hemoglobinuria is the dark red or blackish coffee color of the urine, passed after the onset of the paroxysm, due to the presence of hemoglobin.

In a typical attack, red blood cells are not found in the urine. Foix and Salin[18] and other writers stated that there is some albumin-

15. Macalister, G. H.: The Pathology of Paroxysmal Hemoglobinuria, Quart. J. Med. **2**:368, 1908-1909.

16. Kobler, G., and Obermeyer, F.: Beitrag zur Kenntnis der paroxysmalen Hämoglobinurie, Ztschr. f. klin. Med. **13**:163, 1887.

17. Montagnani, M.: Crises hémoclasique et hémoglobinurie, Presse méd. **29**: 1017, 1921.

18. Foix, C., and Salin, H.: De l'hémoglobinurie globulaire expérimentelle, Arch. de méd. expér. et d'anat. path. **24**:305, 1912.

uria immediately before and after the attack, due probably to the action of hemoglobin on the kidneys. Albuminuria may persist for some days after all traces of hemoglobin have disappeared from the urine, a fact noted by Macalister. Spectroscopic examination will show the absorption bands for metahemoglobin and oxyhemoglobin. All these data were well marked in the case described by me.

Mention already has been made of the function of the liver in disposing of hemoglobin freed in the blood stream during hemolysis. It is probable that the spleen helps the liver in storing products of lysis. There is usually some splenic enlargement, although none was noted in the case described. This storage would account for the rapid regeneration of the red cells following an attack of paroxysmal hemoglobinuria, as the loss of pigment through the urine is not great. Jones and Jones [19] found that the hemoglobin content of the blood plasma reached its peak within four or five minutes after the paroxysm commenced and that a large amount of this liberated hemoglobin was converted into bile pigment. Kaznelson [20] observed that in induced chilling hemoglobinuria the bilirubin peak was reached about an hour or two after chilling when the acute stage of hemolysis was passed.

Donath and Landsteiner Chilling Test in Vitro.—Yorke and Macfie [21] found that in the Donath and Landsteiner chilling test in vitro with a mixture of the patient's serum and his own blood corpuscles, maximum lysis was obtained when the mixture was colled to 0.C. for from five to seven and one-half minutes. Mackenzie [22] verified these data, as well as the observation that the hemolysis was about ten times as great as that resulting after exposure at 0 C. for from one-half to one hour. Smith,[23] in his experiments in vitro, found that the maximum amount of lysis occurred after an exposure of forty-five minutes. In the case described by me, it was found that both during and between attacks the most complete hemolysis was obtained after exposure to a temperature of 0.C. for from five to twenty-five minutes and more especially toward the higher limit.

There is no means of determining what amount of exposure brings on maximum lysis in vivo. Mackenzie, however, found that it was

19. Jones, C. M., and Jones, B. B.: A Study of Hemoglobin Metabolism in Paroxysmal Hemoglobinuria, Arch. Int. Med. **29**:669 (May) 1922.

20. Kaznelson, P.: Beobachtungen ueber paroxysmalen Kälthemoglobinurie, Deutsches Arch. f. klin. Med. **138**:46, 1921-1922.

21. Yorke, W., and Macfie, J. S.: The Mechanism of Autolysis in Paroxysmal Hemoglobinuria, Brit. J. Exper. Path. **2**:115, 1921.

22. Mackenzie, G. M.: The Autohemolysin of Paroxysmal Hemoglobinuria, Proc. Soc. Exper. Biol. & Med. **20**:276, 1922.

23. Smith, R. P.: The Relationship of the Autolysin and the Wassermann Antibody in the Serum of a Hemoglobinuric, J. Path. & Bact. **26**:196, 1923.

not necessary to expose the patient to a temperature as low as 0.C., but that hemolysis occurred on exposure to temperatures of from 8 to 12 C.

Coagulation Time.—The blood coagulation time deserves mention. During attacks it was found to be diminished to from one-half to two minutes; but following and between attacks, it again increased to from twelve to fifteen minutes. Weil and Stieffel [24] also found that the periods of intense hemolysis were those in which the coagulation time was shortest. In the case which they described, the coagulation time was one minute, during the hemoglobinuric crisis, whereas at another time, when the Donath and Landsteiner test gave an entirely negative result, the coagulation time was fifty-five minutes. The diminished coagulation time is usually accompanied by contraction of the clot.

The van den Bergh Test.—During the first attack, on February 15, the reaction to the van den Bergh direct test gave slightly positive results; the indirect test immediately gave a strong positive reaction. On the fourth day after this attack both the tests gave negative reactions. At the beginning of the attack on February 20 reactions to both the tests were strongly positive. These observations are in agreement with those reported by Strominger and Gottfried.[25]

THEORIES OF THE ETIOLOGY OF PAROXYSMAL HEMOGLOBINURIA

Some of the earlier writer on the subject of paroxysmal hemoglobinuria attributed the phenomenon to some change in the blood serum which gave it a hemolytic power over the globules. This foreshadowed the later theory of the existence of a special hemolysis in the serum, which will be discussed. Another early theory of paroxysmal hemoglobinuria called the muscular theory, was especially championed by Camus.[26] This theory attributed hemoglobinuria to the transudation of the muscular hemoglobin into the blood plasma. Corlette [27] described a paroxysmal hemoglobinuria in horses and cattle, brought about by exposure to cold, in which there is a concomitant muscular degeneration. This muscular condition has never been observed, so far as is known, in human beings except in the type of hemoglobinuria following exertion. Corlette thought, therefore, that these two types of the

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24. Weil, E. P., and Stieffel, R.: Bull. et mém. Soc. méd. d. hôp. de Paris **49**:1553, 1925.

25. Strominger, L., and Gottfried, M.: Sur un cas d'hémoglobinurie paroxystique avec recherches de lavoratoire complètes, J. d'urol. **22**:45, 1926.

26. Camus, J., and Pagniez, P.: Hémoglobinurie d'origine musculaire, Compt. rend. Acad. d. sc., Aug. 11 and Nov. 14, 1902.

27. Corlette, C. E.: The Paroxysmal Hemoglobinuria of Horses and Cattle, M. J. Australia **1**:429, 1924.

disease may be similar although they differ from paroxysmal hemoglobinuria due to chilling.

Paroxysmal hemoglobinuria was thought by some authors to be connected with changes in the kidney. Van Rossem [28] was one of the first to write on this subject. He stated that red blood corpuscles were destroyed in the kidney by oxalic acid of the urine. Silvestri [29] declared that the kidney in a pathologic state could secrete substances which had a destructive action on the red corpuscles. Foix and Salin stated that the kidney was involved only secondarily by the free hemolysin in the circulation, due to hemolysis, and that this action produces albuminuria which is always present during crises. The renal theory has been sustained by Achard and Feuille,[30] but it does not explain, however, all the phenomena of globular fragility.

Gilbert, Chabrol and Benard propounded the theory that destruction of the red blood corpuscles begins in the spleen. This organ normally destroys old and changed erythrocytes. In pathologic states, the autolysis in the spleen becomes exaggerated. This function of the spleen has also been emphasized by Pearce, Krumbhaar and Frazier.[32] Nolf pointed out that splenic extract had a specific hemolytic action. Widal and his associates,[33] as well as Foix and Salin and others, however, showed that other organic substances acted similarly.

Paroxysmal hemoglobinuria has been considered by some as the result of a nervous reflex. Murri was one of the first to point out that in this condition there was an abnormal excitability of the vasomotor nerve centers and that cases of paroxysmal hemoglobinuria due to other causes than cold, such as inanition, exertion and menstrual irregularities resulted from a special "hemoglobinuric reflex."

Macalister, assuming that in paroxysmal hemoglobinuria the serum is autolytic, stated that chilling hemoglobinuria begins as an intravascular hemolysis. The hemolysis is not due to surface chilling. Under the action of external cold, impulses are sent to the vessels by the vasomotor arc; that it to say, the hemolytic reflex travels by the same route as the vasomotor reflex. Assuming a potential autohemolytic

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28. Van Rossem, P. C.: Paroxysmal Hemoglobinurie, Amsterdam, 1877.

29. Silvestri, T.: Delfattore renale in certi casi di emoglobinurie parossistica, Policlinico **28**:1203, 1921.

30. Achard, C., and Feuillie, E.: Contribution à l'étude de l'hémoglobinurie expérimentelle, Arch. de méd. expér. et d'anat. path. **23**:529, 1911.

31. Gilbert, A.; Chabrol, E., and Benard, H.: Sur la pathogénie de l'hémoglobinurie paroxystique, Presse méd. **20**:1001, 1912.

32. Pearce, Krumbhaar and Frazier, cited by Jones (footnote 19).

33. Widal, F.; Abrami, P., and Brule, M.: Pluralité d'origine des ictères hémolystiques, Bull. et mém. Soc. méd. d. hôp de Paris, Nov. 20, 1907.

factor in the blood and that the reflex passes, as stated, through the vasomotor nerve fibers, Macalister admitted that there is still a missing link; the nerve endings are situated in the vessel wall and do not have direct communication with the blood itself; evidence does not exist that any secretion is poured out by the endothelial cells in response to vasomotor stimuli.

Foix and Salin stated the belief that in chilling hemoglobinuria, in addition to the changes in the blood serum, a special fragility of the red corpuscles must be assumed, and that such a special fragility in these cases can be demonstrated even with normal serum. Weil and Stieffel also considered that the classic reaction in chilling hemoglobinuria shows a special fragilty of the corpuscles. Hertz and Marmot [34] also supported the view of a special globular fragility. Since the serum of patients with paroxysmal hemoglobinuria, however, is both isolytic and autolytic, that is, it hemolyzes the corpuscles not only of the patient, but of any normal subject, it does not seem necessary to assume any special vulnerability of the red corpuscles. The fragility observed during attacks is apparently an effect of the hemolyzing agent itself.

In the case described in this paper, special tests were made for globular fragility. Immediately after the attack on February 15, the fragility was 51 and 40 per cent; on February 19, the fourth day of the attack, it was 47 and 38 per cent. On February 20, during a new attack, it was 56 and 43 per cent, and on the day following, 48 and 36 per cent. It was 46 and 37 per cent, practically the same figure as the previous one, on April 2 during an interval between attacks, and on April 7, during a new attack, it again reached 52 and 41 per cent.

The foregoing figures suggest that there is a change in the globular fragility during the attacks. At the beginning of and during the attack the fragility is increased both as to the superior and inferior limits; it sinks to normal, however, between attacks. This confirms the view that normally the red corpuscles of patients with paroxysmal hemoglobinuria are not essentially fragile. Strominger and Gottfried, in the case which they reported, found that during an attack the normal figures for globular fragility increased slightly toward the lower limit but diminished toward the superior limit.

At the present time the various etiologic factors associated with paroxysmal hemoglobinuria have been reduced to two principal theories: namely, (1) that the condition is due to the presence of a special hemolytic amboceptor in the serum of the patient which has the capacity of sensitizing red blood corpuscles at a low temperature; or (2) that it is the result of anaphylactic shock or a hemoclasia due to cold only.

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34. Hertz, R., and Marmot, A.: De l'hémoglobinurie paroxystique, Arch. de méd. expér. et d'anat. path. **24**:561, 1912.

THE SPECIAL HEMOLYSIS THEORY

Donath and Landsteiner were practically the first to assume and show the existence in the blood serum of patients with paroxysmal hemoglobinuria of a thermolabile autohemolysin and isohemolysin or amboceptor which, on chilling, becomes fixed to the red corpuscles, sensitizes them and, by permitting the complement to be attracted to the corpuscles at a higher temperature, renders hemolysis possible.

Later writers assumed the existence of a special hemolysin and believed that it could be exhausted by continuous lytic action, or even separated from the patient's serum.

Hoover and Stone [35] stated that hemolytic serum contained two factors, one stable and capable of being inactivated by exposure to a temperature of 56 C. for twenty-five minutes; this factor was common to all serums and corresponded to Ehrlich's complement. The second factor was found only in paroxysmal hemoglobinuric serum and was resistant to a temperature of 56 C. for twenty-five minutes. It corresponded to the amboceptor of Ehrlich and could be fixed in the biochemical union to the red blood corpuscles and exhausted from the hemoglobinuric serum if a sufficient number of corpuscles were suspended in the serum and the mixture exposed to a low temperature for one hour. These authors claimed that they had experimentally demonstrated this fact by adding, in two stages, ten drops of a 10 per cent suspension of red blood corpuscles to 1 cc. of serum and exposing the mixture to cold for an hour. The amboceptor was exhausted from the inactivated hemoglobinuric serum.

Burmeister [36] claimed to have isolated from the blood in these patients with hemoglobinuria the special amboceptor or hemolysin which induced the positive response to the Wassermann reaction and which was considered generally as syphilitic. He asserted that when this amboceptor was added to normal serum, it gave a positive Wassermann reaction.

On repeating Burmeister's technic with the serum of the patient previously described, I found that the Wassermann reaction with normal serum was not positive as Burmeister found, but negative.

Burmeister's technic was used in examining the serum as follows: Five cubic centimeters of hemoglobinuric serum was added to 1 cc. of 100 per cent of erythrocytes and 85 per cent of physiologic solution of sodium chloride. The mixture was left for one hour in water of from 1 to 3 C. in temperature. The sensitized erythrocytes were then washed

35. Hoover, C. F., and Stone, C. W.: Paroxysmal Hemoglobinuria, Arch. Int. Med. **2**:392 (Nov.) 1908.

36. Burmeister, J.: Zur Beeinflussung der Kältehamoglobinurie durch unspezifische wirkende Salzlosungen, Ztschr. f. klin. Med. **92**:134, 1921; Ueber paroxysmale Hämoglobinurie und syphilis, ibid. **92**:19, 1921.

with a 3 per cent physiologic solution of sodium chloride so as to wash out all traces of the serum; 3 cc. of a physiologic solution of sodium chloride was then added, and the mixture was kept at 37 C. for two hours. According to Burmeister a dissociation of amboceptor and erythrocytes follows; after centrifugalization, the amboceptor was held in a physiologic solution of sodium chloride. This was added to normal serum. The process was repeated twice, but the Wassermann reaction was negative.

Burmeister's technic was then modified by adding a one-half, and a saturated, solution respectively of ammonium sulphite instead of sodium chloride. In this as in the original Burmeister test on the patient's serum, the Wassermann reaction was negative.

THE ANAPHYLACTIC THEORY

The French school especially considers paroxysmal hemoglobinuria as a kind of auto-anaphylactic shock or autocolloidoclasia.

In 1907, Besredka [37] observed certain vascular phenomena accompanying anaphylactic shock; namely, a rapid fall in arterial pressure, leukopenia, diminution of blood platelets and a reversal of the leukocytary formula. These observations were confirmed later by Biedl, Krauss [38] and others.

Michelli,[39] in 1910, was the first to consider paroxysmal hemoglobinuria as an anaphylactic phenomenon. He observed that cold caused a colloid disequilibrium translated by hemoclasia.

Widal, Abrami and Brissaud,[40] in 1913, found that the vascular phenomena of anaphylaxis coincided exactly with the appearance of the first symptoms of paroxysmal hemoglobinuria. They also found other signs: disturbance of coagulation time, lowering of the index of refraction of the serum and absence of retraction of the clot. To this whole syndrome, which could be induced by lowering the temperature of the blood of a patient with paroxysmal hemoglobinuria to 0 C. for some time, they gave the name of hemoclasic crisis. They believed that this was explained by a hypothesis already put forward by Widal and Rostaine,[41] namely, the existence, in labile equilibrium, of a complex formed by amboceptor, antihemolysin and complement in the serum of paroxysmal hemoglobinuric patients under ordinary circum-

37. Besredka: Anaphylaxie et antianaphylaxie, Paris, Masson & Cie., 1907.

38. Biedl and Krauss, cited by Macalister (footnote 15).

39. Michelli, F.: Osservazioni e ricerche sull' emoglobinuria parossistica a frigore, Clin. med. ital. **54**:256, 1915.

40. Widal, F.; Abrami, P., and Brissaud, E.: Recherches sur l'hémoglobinurie paroxystique à frigore, Compt. rend. Soc. de biol. **65**:432, 1913.

41. Widal, F., and Rostaine: Sérothérapie preventif de l'attaque d'hémoglobinurie paroxystique, Compt. rend. Soc. de biol. **58**:397, 1905; ibid. **60**:406, 1906.

stances. This equilibrium could be brusquely dissociated by cold which paralyzed the antihemolytic substance in the serum. It will be noted that the existence of a special hemolysin was not questioned.

Montagnani also believed that paroxysmal hemoglobinuria had an anaphylactic origin, and that it could be brought on by the sudden action of cold independently of the intervention of any antigen. In the case which he described he found many of the anaphylactic phenomena present.

There appears to be but little doubt that there is similarity between many of the phenomena observed during anaphylactic or protein shock and the crisis of paroxysmal hemoglobinuria. In the case described by me, there was a marked fall in the arterial pressure at the onset of the attack, a marked diminution of clotting time immediately following the onset of the attack, and a marked increase in the number of blood platelets, but a diminution in the intervals between attacks. A leukocytosis rather than a leukopenia was observed to follow the onset of attacks. The leukopenia in the cases described in the French literature seems to have occurred just prior to the onset of attack. It is possible that some of the other anaphylactic phenomena might have been present also just before the attack, as in the case described by Enneking [42] in which the hemoclasic crisis preceded the attack.

It is possible that cold alone may bring on a hemoclasic crisis, but the presence of a factor in the blood, which is responsible for the hemolytic action seems difficult to deny. In fact, Widal does not deny the specificity of the autohemolysin of Donath and Landsteiner and its association with the hemoclasic crisis.

SYPHILIS AND AUTOHEMOLYSIS

Most authors agree that the presence of a special autolysin in the blood serum of patients with paroxysmal hemoglobinuria is the result of the action of the syphilitic virus. Blumer, in his recently issued textbook on bedside diagnosis, said plainly, "it is now known that this disease (paroxysmal hemoglobinuria) is due to syphilis."

As long ago as 1874, Wilbuscevik [43] observed that in cases of syphilis the red blood corpuscles diminished and the white corpuscles increased. Later investigators, such as Konried,[44] found that the hemoglobin content of the corpuscles was attacked by the syphilitic virus. Another common view was that the stroma of the red cells was so modified by syphilis that it was not any longer capable of holding the hemoglobin firmly.

42. Enneking, J.: A Special Form of Paroxysmal Hemoglobinuria, Nederl. Tijdschr. f. Geneesk. **69**:1526, 1925.

43. Wilbuscevik, cited by Macalister (footnote 15).

44. Konried: Ueber Veränderungen des Blutes bei Syphilis, Wien. med. Wchnschr. **42**:1971, 1892.

Justus [45] found that he could produce hemolysis in syphilitic patients by stasis alone without exposure to cold. Murri was one of the first to connect syphilis clearly with paroxysmal hemoglobinuria and to institute antisyphilitic treatment.

It is not certain that the pathogenic agent in paroxysmal hemoglobinuria is syphilitic only. Burmeister, who collected 207 cases of the disease, found that only 30 per cent of the patients showed signs of syphilis. Macalister stated that only 60 per cent of patients with paroxysmal hemoglobinuria gave a history of syphilis. In 76 of Burmeister's 207 cases, however, in which the making of a Wassermann test is recorded, 95 per cent of the reactions were positive. Salen [46] stated that in 95 cases of paroxysmal hemoglobinuria, reported since 1904, a history of syphilis was given in 85 per cent of the cases in which a history was taken and that the Wassermann test gave positive results in 95 per cent of these.

Burmeister asserted that in chilling hemoglobinuria the Wassermann reaction might be positive even in the absence of syphilis, and that this positive reaction was induced by the special amboceptor which he claimed to have separated from the patient's serum. Burmeister considered that the removal of the autolysin, by treating the serum with red corpuscles in the cold, led to the disappearance of the Wassermann reacting body from the fluid. Smith, however, repeating the technic of Burmeister, found, on the contrary, that the removal of the greater part of the autolysin produced but little diminution in the capacity of the serum to fix complement in the Wassermann reaction. Salen also found that the hemolytic amboceptor causing the Donath and Landsteiner reaction does not influence the Wassermann reaction. Mackenzie found that the Wassermann reacting substance and the Donath and Landsteiner chilling amboceptor were distinct serologic entities. In the one of his three cases which had the highest titer of chilling amboceptor, the Wassermann reaction was weakest. The results obtained by me with Burmeister's technic have already been given.

Hannema and Rytma,[47] like Burmeister, admitted the possibility in these cases of a positive Wassermann reaction without syphilis and stated the belief that there is a possibilty that the substance which is produced by the organism of syphilis and causes fixation of complement, and a positive Wassermann reaction can be produced by some other agency in paroxysmal hemoglobinuria.

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45. Justus: Orvosi hetil. **38**:285, 1894.

46. Salen, E. B.: Studien über die Kältehämoglobinurie, Acta med. Scandinav. **11**:62, 1925.

47. Hannema, L. S., and Rytma, J. R.: Some Investigations into a Case of Paroxysmal Hemoglobinuria, Lancet **2**:1217, 1922.

On the other hand, cases have been recorded in which the Wassermann reaction was negative in paroxysmal hemoglobinuria.

In a case described by Roch and Liengme,[48] the patient gave a typical reaction to the Donath and Landsteiner chilling test. The Wassermann test, however, gave negative results, and hemoglobin was not found in the serum during any of the attacks. In this case also induced attacks appeared later than usual following exposures but lasted longer than usual.

The fact also remains that few syphilitic patients when exposed to severe cold suffer from paroxysmal hemoglobinuria. Donath and Landsteiner obtained a positive reaction in only four of eighty-five patients with paresis. On the other hand, Kumagai and Inoue [49] were able to demonstrate the presence of hemolysin in parasyphilitic patients and those in the tertiary stage, and could induce hemoglobinuric crises in such patients by giving them cold foot baths.

The exact underlying cause for the presence of a special hemolysin in cases of paroxysmal hemoglobinuria cannot be considered as settled. In the case described in this paper, owing to the repeated negative reactions in the patient's father and mother and a strongly positive reaction in the child, I was inclined to seek the cause of the alteration in the blood in the abortive attack of scarlet fever which was mentioned in the history. The later finding of a positive Wassermann reaction in the mother, however, dispelled this view, and I am forced to admit that syphilis is connected with the hemolytic factor in this case.

TREATMENT

On the assumption that the essential factor in the etiology of paroxysmal hemoglobinuria is syphilis, the majority of investigators have favored antisyphilitic treatment. Kumagai and Namba [50] have recently reported the cases of fourteen patients with paroxysmal hemoglobinuria who were submitted to antisyphilitic treatment; ten of these were clinically cured. The titer of the autohemolysin was diminished by the antisyphilitic treatment. In the case reported by Ardin-Delteil [51] and his associates, antisyphilitic treatment did not change the Wassermann reaction, although the patient could be exposed to cold without getting attacks of hemoglobinuria. In the case described by me, anti-

48. Roch, M., and Liengme, A.: Bull. et mém. Soc. méd. d. hôp. de Paris **46**:1737, 1922.

49. Kumagai, T., and Inoue, B.: Beitrage zue Kenntnis der paroxysmale Hämoglobinurie, Deutsche med. Wchnschr. **38**:361, 1912.

50. Kumagai, T., and Namba, M.: Deutsches Arch. f. klin. Med. **156**:257, 1927.

51. Ardin-Delteil, P.; Derrieu, and Azoulay, R.: Un cas d'hémoglobinurie paroxystique "a frigore," Bull. et mém. Soc. méd. d. hôp. de Paris **41**:1562, 1922.

syphilitic treatment has been entirely unsuccessful either in lessening or abolishing the positive Wassermann reaction or the hemoglobinuria.

Widal and his associates, in accordance with their anaphylactic theory of paroxysmal hemoglobinuria, introduced an anticolloidoclasic treatment by the intravenous injection of the patient's own serum which acts as a foreign protein. They reported good results. Montagnani, who was satisfied that in the case which he observed the etiology was in accordance with Widal's theory, injected 40 cc. of the patient's serum in seven injections. He found that the hemoglobinuric crises which followed were more frequent and more intense than those which had preceded this treatment. On the other hand, he found antisyphilitic treatment entirely satisfactory. Meyer [52] and Ardin-Delteil and his associates also failed to obtain any satisfactory results from autoserotherapy but found antisyphilitic treatment satisfactory.

Weil and Chevallier [53] found that the Donath and Landsteiner test became negative when a physiologic solution of sodium chloride was added to the patient's serum before it was mixed with the patient's red corpuscles. Citrate of sodium had the same effect as sodium chloride.

Burmeister also found that cholesterol, administered by vein or mouth, modified the physical condition of the blood of these patients so as to render it resistant to destruction by chilling, acting in the same way as hypertonic solution of sodium chloride in vitro.

CONCLUSIONS

1. So-called paroxysmal hemoglobinuria, especially the type caused by chilling, is not really paroxysmal in character. The term is a misnomer, as the condition can always be produced under certain well defined circumstances in patients subject to it.

2. The condition apparently is due to the presence of a definite special hemolysin in the blood serum of the patient which becomes active at low temperatures.

3. The underlying factor responsible for the presence of the special hemolysin is probably syphilis. It does not seem unreasonable, however, to suppose that toxins arising from other infections may be capable of bringing about this condition.

4. It is open to reasonable doubt, however, whether the positive Wassermann reaction, observed in the great majority of these cases, is really indicative of syphilis or merely due to the changed condition of the blood serum.

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52. Meyer, E., and Emmerich, E.: Ueber paroxysmale Hämoglobinurie, Deutsches Arch. f. klin. Med. **96**:287, 1909.

53. Weil, P. E., and Chevallier, P.: Influence de certaines solutions saline sur hémoglobinurie paroxystique, Compt. rend. Soc. de biol. Paris **75**:475, 1913.

5. Some of the phenomena observed during attacks of paroxysmal hemoglobinuria have been ascribed to anaphylactic shock; this is not incompatible with the presence of a special hemolysin in the blood serum. This view is not concurred in by the majority of investigators.

6. The only treatment that gives any favorable results is antisyphilitic; but this is frequently unsuccessful, as in the case reported.

7. The laboratory data in a typical case, in a child, are given and are practically in agreement with the data in other typical cases described in the literature.

DEGENERATION OF THE CEREBRAL CORTEX IN THE COURSE OF PERTUSSIS

RÉSUMÉ OF THE LITERATURE AND REPORT OF A CASE WITH ANATOMIC OBSERVATIONS *

FRANK R. FORD, M.D.

BALTIMORE

A great variety of neurologic disturbances are known to occur in the course of pertussis. Among these the commonest are convulsions, cerebral palsies of various types and visual disturbances. These symptoms may be of brief duration or may persist. The older neurologists were accustomed to attribute such complications to cerebral hemorrhages resulting from the cerebral congestion which occurs during the paroxysms, but it is well known that hemorrhages may be absent in some cases and even when present may be insufficient to explain the clinical picture. This fact led to the theory that cerebral edema or "serous meningitis" was the pathologic basis of the nervous manifestations in pertussis, and Neurath [1] was able to demonstrate mild meningeal changes in fatal cases.

In 1924, Husler and Spatz [2] published an article which threw new light on the subject. These investigators made a careful histologic study of the nervous system of two children who had died in convulsions following pertussis. One lived only three days after the onset of the convulsions, dying in status epilepticus, and the other child died after three weeks of a terminal pneumonia. The spinal fluid was entirely normal in each case. The anatomic changes are described as follows:

> The lesions were the same in each case. No hemorrhages were to be found in the meninges or nervous tissue. The inflammatory changes which Neurath describes in the meninges were confirmed. The arachnoid mesh was somewhat loosened, the fixed tissue cells somewhat increased, and large wandering cells as well as lymphocytes were found in the connective tissue trabeculae. In case 1, there were also some leukocytes present. The changes were most outspoken in the basilar region. Nowhere did the cell infiltration extend to the adventitial sheath of the cortical vessels or even to the pial opening of this sheath. The inflammatory changes were so slight that one may well question whether the term meningitis might be properly applied. In contrast to the slight lesions found in the meninges, severe and characteristic lesions were found in the brain itself. These were not inflammatory. A number of cortical nerve cells showed a typical

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1. Neurath: Arb. a. d. neurol. Inst. a. d. Wien. Univ. **11**:258, 1904.
2. Husler and Spatz: Ztschr. f. Kinderh. **38**:428, 1924.

degenerative process, but other cells of the cortex suffered little or no change. The cytoplasm of the affected cells stained intensely with eosin and had completely lost its affinity for basic dyes. In Nissl stains nothing was to be seen of these cells except the characteristic nuclei, the swollen and decolorized nucleoli of which were surrounded by metachromatically stained chromatin granules. These changes in the nerve cells were identified with the so-called "homogenisierende" cell changes which Spielmeyer has described in the Purkinje cells as a result of typhus fever and other infectious diseases. There is no doubt that this process is not reversible and leads to the death of the cell. The result is a more diffuse or focal cell loss. In the first acute case, the "homogenisierende" cell changes were found in a large percentage of the cortical cells, but in case 2, in which the process was of longer duration, the number of cells affected was not so large, but more karyolysis and karyorrhexis were found. There were also many medulated fibers in the cortical fiber bundles which showed signs of degeneration. The glia was proliferated and in some regions contained numerous lipoid granules. The blood vessels were dilated and engorged with blood, and there was some proliferation of the fixed cells in the vessel wall. These regressive changes in the nerve cells and the progressive changes of the glia were found throughout the cortex, reaching their maximum degree in the cornu ammonis. In case 1, the process involved the corpus striatum which was as severely affected as the cortex. The lower parts of the brain stem were intact, but in case 2 there were typical changes in the Purkinje cells of the cerebellum and in the dentate nuclei. The white matter was everywhere intact.

Neubürger [3] and Singer [4] have since demonstrated the same lesions described, although the former is inclined to attribute them to hypothetical air emboli due to rupture of the lung alveoli in paroxysms of coughing.

In March, 1928, Jochims [5] published the clinical history and pathologic observations in the case of a little girl who developed convulsions and bilateral rigidity in connection with pertussis. This case is of such interest that it will be abstracted in brief:

A girl, aged 14 months, developed convulsions and rigidity two weeks after the onset of pertussis. When first seen she was deeply comatose, and there was general rigidity of the muscles. The temperature ranged from 39 to 40 C. (102.2 to 104 F.). Frequent twitchings of the muscles were present. The knee jerks were absent. The Babinski sign was not elicited. Examination of the spinal fluid showed: cells, 15; Pandy, 0; pressure, 390 mm. The cell count rose to 58 and then to 200 on the fifth day after admission, and there was an increase of globulin and film formation at the same time. However, after two days the cell count had fallen to 18, and the globulin was normal. Death occurred from pneumonia after an illness of fourteen days, during which the child was comatose and rigid and suffered frequent convulsions. At autopsy there was a small hemorrhage in the right occipital lobe the size of a cherry. Microscopically, there were found numerous small areas of cell loss in the cortex, as described by Husler and Spatz. In hematoxylin and eosin stains, the so-called homogenisierende cell changes

3. Neubürger: Klin. Wchnschr. **4**:113, 1925.

4. Singer: Klin. Wchnschr. **6**:994, 1927.

5. Jochims, J.: Ztschr. f. Kinderh. **45**:326, 1928.

(staining of the cytoplasm by eosin) were apparent. Fat stains revealed lipoid droplets in the elongated Hortega cells in the cortex which were especially striking in the cornu ammonis. The basal ganglia were unchanged except for a single focus of perivascular cell collection. The meninges were free from pathologic alterations.

REPORT OF CASE

Through the kindness of Dr. Edwards Park I am enabled to publish the history of a similar case which was observed in the Harriet Lane Home for Children, in a girl of 20 months who developed convulsions and general rigidity five weeks after the onset of pertussis. These symptoms persisted. The cerebrospinal fluid was normal. Death occurred from secondary infections after four months. Autopsy showed diffuse symmetrical atrophy of the cortex.

History.—A. H., a colored girl, aged 20 months, was brought to the Harriet Lane Home on Feb. 29,1928, because of general stiffness of the muscles which had suddenly developed during pertussis. The patient was the sixth child of a healthy family and had never been ill in any way before the present illness. During December, 1927, the patient developed a cough which soon became paroxysmal. The child vomited frequently; the appetite was poor, and she lost weight rapidly. The mother thought that there was some fever at night. About January 7, the patient had a spasm during which she was unconscious; the eyes rolled up, and the arms and legs were stiff. She never seemed to recover from this and stayed in bed afterward. Her arms and legs were weak and stiff, and she made no attempt to talk. Gradually she grew more rigid and soon was quite helpless. Her mother was an ignorant negress, but seemed to be definite about the essentials of the history.

On examination, the child was undernourished and poorly developed. She lay stiffly extended and apparently unconscious. Her eyes were open, but she seemed to see nothing. At times there were paroxysms of coughing which ended in typical "whoops." The right arm was adducted, extended at the elbow, pronated at the wrist and strongly flexed at the wrist and finger joints. The left arm was flexed at the elbow, but was otherwise in the same position as the right arm. Both legs were extended at all joints and tended to remain crossed. This strange posture persisted unchanged throughout the course of the illness. The entire musculature was rigid and firm, and considerable force was necessary to carry out any passive movement. The child did not respond to any visual or auditory stimuli, but would whine when pinched. Practically no spontaneous movements were observed. The pupils were dilated, but reacted well to light. There was no squint, and the optic nerve heads and retinas were normal. The face was symmetrical, and the child could swallow when food was placed in her mouth. She made no attempt to talk. All the tendon reflexes were exaggerated, but there was no ankle clonus, and plantar stimulation produced plantar flexion. The pharynx was only slightly injected. A small ulcer was present on the frenum of the tongue. The ears were normal. The lungs were normal except for a few bronchial râles. The heart and abdomen were normal. The temperature was 98 F.

The red blood cells numbered 5,200,000; hemoglobin, 74 per cent; white blood cells, 7,000; polymorphonuclears, 41 per cent; lymphocytes, 54 per cent, and mononuclears, 5 per cent. The vaginal smear was negative. The Wassermann reaction of the blood was negative. The cerebrospinal fluid was clear and showed 1 cell. The Pandy and the Wassermann tests were negative; the mastic curve was 00000000000. The tuberculin skin test (0.1 mg.) and the Schick tests were negative.

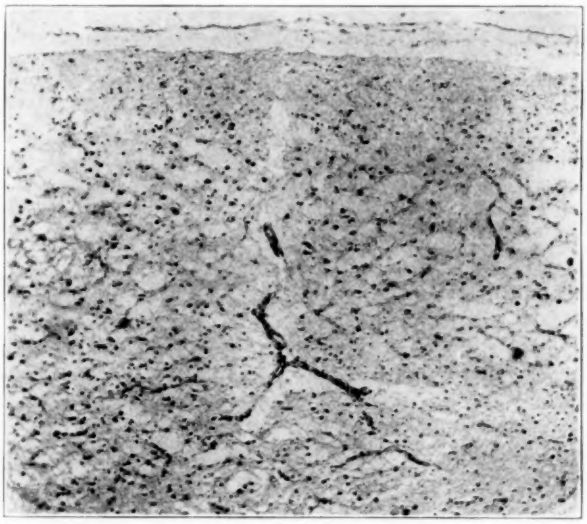
A culture from the throat was negative. The urine showed a trace of albumin, but was otherwise normal.

On March 27, the patient's temperature had varied between 38 and 40 C. (100.4 and 104 F.) for the last ten days. The urine was clear. The ears and chest were normal. The throat was clear. The general condition was unchanged.

On April 4, the coughing had practically ceased. The child showed slight movements of the hands, but lay in the same position and was rigid. The temperature had been normal for a week, but the patient had lost weight.

On May 15, she had fever again. This time, partial consolidation of the upper lobe of the right lung was found.

On May 29, the left shoulder joint was swollen. Seven cubic centimeters of pus was aspirated. The cerebrospinal fluid was clear; it showed: 1 cell; the



Extensive loss of nerve cells in the postcentral cortex. The second, third and fourth cortical layers are reduced to a spongy glial tissue. The pia-arachnoid is unalterated, and a small cortical arteriole shows no adventitial infiltration.

Pandy test, negative; mastic curve, 000000000; Wassermann, negative; sugar, 38 mg. The child could not swallow and had to be fed by gavage.

On June 14, the left shoulder joint was incised, and 200 cc. of pus was removed. Hemolytic streptococci were obtained on culture.

On July 8, decubitus ulcers were present. Progressive emaciation occurred, and finally the patient died.

Anatomic Observations.—Marked emaciation, lymphoid hyperplasia, decubitus ulcers, pleural adhesions, suppurative arthritis of the left shoulder joint, parotitis and general atrophy of the cerebral convolutions were found on gross examination.

The meninges were delicate, and no meningeal hemorrhages were seen. The vessels at the base were normal. There was diffuse atrophy of the cerebral convolutions which affected both hemispheres symmetrically. This was most severe in the frontal region where the wasting was so extreme that the depths of the sulci were revealed. On section it was apparent that the entire brain was somewhat

shrunken, although the cortex was more affected than the white matter. No hemorrhages were found. The ventricles were slightly dilated.

The histologic picture was everywhere the same and varied only in degree. In brief there was an almost universal loss of nerve cells. Sections of the frontal cortex, which had suffered the greatest injury, perhaps, revealed almost total disappearance of nerve cells. The cell layers of the cortex were represented by a glial reticulum composed of the fibrous processes of large astrocytes. These astrocytes were somewhat swollen, and a few fine lipoid granules were sometimes seen in their cytoplasm. Their numbers were not greatly increased and indeed, the glial reaction was moderate. As a result, the reticulum was delicate and often collapsed, reducing the cortex to a small part of its proper thickness. A few fat-laden gitter cells were to be seen in the interstices of this tissue. The fiber layers of the cortex were preserved to an unexpected degree and showed only partial demyelinization. Long rows of round glial nuclei each surrounded by a clear zone of unstained cytoplasm were seen between the fiber bundles. These cells are the so-called oligodendroglia undergoing acute swelling. The precentral cortex and the paracentral lobe showed severe loss of cells in the second and third cortical layers, but the giant pyramid cells were for the most part intact. In general, nerve cells either were completely degenerated and represented by an empty space or presented a normal appearance. The acute cell changes described by Husler and Spatz were not seen. The posterior central convolutions were reduced to a mere glial sponge and were completely collapsed. The occipital and temporal lobes were likewise severely altered. In general the base of the convolution suffered more than the apex and the superficial layers of the cortex more than the deep layers. The cornu ammonis, in which Husler and Spatz found the most severe lesions in their cases, showed almost complete destruction of the cell layer. The hippocampal gyrus was affected to a similar degree, and most of the cell clusters were greatly reduced. The basal ganglions were involved but not to a comparable degree. In the thalamus and lenticular nuclei there was some loss of nerve cells, and some large ganglion cells showed displacement of the nucleus and vacuolation of the cytoplasm. In the cerebellum a moderate percentage of the Purkinje cells were missing, and the granule layer was greatly thinned out in places. The brain stem and spinal cord were unaltered, and there was no degeneration in the pyramids. No definite changes were found in the meninges. The blood vessels seemed quite normal, although the perivascular spaces were often widened by the shrinking of the tissues. No lymphocytes, and, indeed, no cells of any type, were to be seen in the adventitia of the small blood vessels. The process was diffuse and symmetrical on the two sides. It bore no demonstrable relation to the blood supply and could be regarded only as the result of a toxic process or of a diffuse cortical inflammation which had receded.

SUMMARY

The case history of a child, aged 20 months, who developed cerebral diplegia after pertussis is briefly presented. This was found to be due to a great loss of cortical nerve cells unrelated to vascular disturbances or inflammatory processes. This condition was first described by Husler and Spatz and probably represents the anatomic basis of many of the nervous complications of pertussis. The lesions are quite different from those which have been found in the nervous system following measles and vaccinia.

CAPILLARY BRONCHITIS

THE EFFECT OF THE ADMINISTRATION OF OXYGEN ON THE HEALING PROCESS *

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Boothby and Haines [1] have shown that the greatest benefit from the administration of oxygen in cases of cyanosis occurs when the pulmonary lesion has not advanced beyond the stage of congestion and edema. By increasing the oxygen content of the alveolar air, and thus of the blood, the anoxemia is relieved, and the body is better able to resist infection. They have noted that the characteristic drop in temperature which follows shortly after the patient is placed in the oxygen chamber is more pronounced when frank pneumonia has not developed. This is explained by the fact that at this stage the elevated temperature is in a great measure due to the anoxemia. It would appear, therefore, that patients with capillary bronchitis are benefited by the early administration of oxygen.

Fulminating capillary bronchitis is characterized by the sudden development of marked dyspnea, cyanosis and high temperature, coming on during the course of an acute infection of the respiratory tract, practically without clinical manifestations in the chest. If the patient does not succumb during the first two or three days, there is a fair chance of recovery. The bronchioles are generally involved, air is almost completely shut off from the alveoli, and death results from the anoxemia, combined with the toxemia of the infection.

The pathologic process starts with swelling of the mucous membrane of the small bronchial tubes, pouring out of mucus, edema and congestion of the walls and desquamation of the epithelial lining. An inflammatory exudate, consisting of polymorphonuclear leukocytes, a few mononuclear leukocytes, erythrocytes and epithelial cells, appears within the lumen. Death may supervene, or the inflammation may spread to contiguous alveoli, especially to those about the terminal bronchioles. Fibrin is formed in the exudate; some portions of the lungs become

* Submitted for publication, Nov. 28, 1928.

* Work done in the Section on Pediatrics, The Mayo Clinic.

* Read before the Northwestern Pediatric Society, Rochester, Minn., July 14, 1928.

1. Boothby, W. M., and Haines, S. F.: Oxygen Therapy, J. A. M. A. **90**:372 (Feb. 4) 1928.

atelectatic, and in others emphysema develops. Healing is accomplished by liquefaction with absorption and partial expectoration of the exudate. Occasionally autolysis does not take place, and fibrous tissue gradually replaces the fibrinous exudate, as in lobar pneumonia. This general description varies with the type of organism producing the disease and the inherent resistance of the patient.

In the following case, life was maintained for almost four weeks by the administration of oxygen. At necropsy, a unique pathologic process was found.

REPORT OF CASE

A boy, aged 11 months, had been ill with an acute infection of the respiratory tract for a week before entering the hospital. Three days before entrance he had begun to breathe rapidly; the temperature mounted, and there was severe coughing.

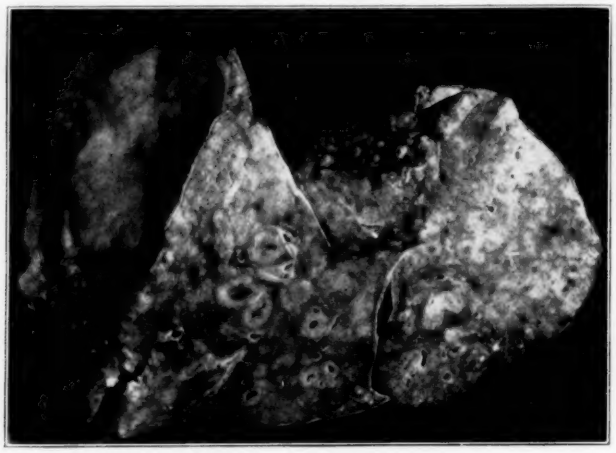

Fig. 1.—Section of the lung.

On admission, he was in partial collapse. There was marked cyanosis, the respirations were rapid and labored, the temperature was 106 F. and the pulse rate 168.

Examination of the chest revealed diffuse high pitched râles over the bases of both lungs, but no dulness. The ear drums were slightly red; the tonsils and pharynx were inflamed. The child was placed in an oxygen tent, and almost immediately the cyanosis cleared up; the temperature dropped, but on succeeding days it fluctuated between 100 and 104 F. The pulse rate remained high. On the twelfth day in the hospital, otitis media developed. Myringotomy resulted in the drainage of a small amount of purulent matter. Ten days before the death of the patient, dulness was noted in the lower left side of the chest posteriorly, with tubular breathing over this area. A similar condition, although not so marked, was noted in the right side a few days later. Free fluid was never demonstrated in the chest. The patient could not be removed from the oxygen tent without the immediate development of cyanosis, marked dyspnea and other signs of collapse. Even while the patient was in the oxygen tent, several critical periods occurred in which stimulants apparently prevented death. The child died after he had been in the oxygen tent for twenty-six days.

At necropsy, bronchopneumonia was not found, and it was impossible to explain the cause of death from the gross examination. Free fluid was not present in the pleural cavities, but there was a small amount of fibrinous exudate over the lateral lower portions of the lungs on each side of the chest. The lungs were pinkish gray over the upper anterior portions, and purple in the lower and posterior

Fig. 2.—Process of organization within the lumina of the bronchioles: *a*, invasion of lumen by connective tissue; *b*, pus; *c*, connective tissue, and *d*, total obliteration.

Fig. 3.—Lumen of bronchial tube almost completely filled with young connective tissue.

portions. Numerous areas of subpleural hemorrhage were present on the surfaces. Emphysema was found along the anterior margins of the upper lobes of the lung, and in the other portions crepitation was diminished or absent. The posterior and lower portions of the lungs were of a meaty consistency, and small, firm, discrete

nodules could be palpated throughout. Section showed these nodules to be firm, gray areas from which pus could not be expressed (fig. 1).

It was not until the sections were examined microscopically that the cause of death was discovered. A process had taken place within the lumina of the bronchioles with the result that many places were entirely filled with newly formed connective tissue completely shutting off the passage of air to the alveoli (figs. 2 and 3). Occasionally a lumen was seen that consisted of only a narrow slit between the margin of the fibrous tissue and the wall of the bronchiole. Capillary blood vessels filled with erythrocytes were seen in the newly formed tissue. In many places only small sections of the walls of the bronchiole remained, and in others they had been destroyed completely, leaving only collections of exudate or fibrous tissue to show the site of a former bronchiole. There were large areas in which the alveoli were atelectatic. An occasional area of emphysema was seen.

By the continuous administration of oxygen, life was prolonged and an opportunity afforded for this extraordinary healing process to take place in the bronchioles. Many of these small air passages to the alveoli were occluded, and death resulted, probably from asphyxiation. Apparently a natural process of healing caused death.

SUMMARY

The early administration of oxygen should be beneficial in the treatment of capillary bronchitis. In the case described, life was prolonged twenty-six days by the continuous administration of oxygen. An unusual healing process took place; many of the bronchioles were plugged by fibrous tissue to a point of occlusion. Death apparently was due to asphyxia as the result of this remarkable attempt at healing.

INFANT BEHAVIOR IN RELATION TO PEDIATRICS*

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Historically, the psychology of infancy has had two sources of origin: one in speculative philosophy, the other in physiology. One may welcome any opportunity to emphasize the potential status of developmental psychology as a natural science in close association with the medical sciences.

THE SCIENTIFIC STUDY OF CHILD DEVELOPMENT

At the present time, the study of child development is in an interesting phase of transition, both in America and abroad. Centers of child research have sprung up in the past ten years at points as far flung as Chicago, Iowa, New York, California, Geneva, Vienna and Moscow. The National Research Council in 1923 took the first steps toward the organization of a committee on child development for the promotion, correlation and integration of research relating to the growth of the child. The national research conferences sponsored by this committee have recognized and brought together such varied interests as biochemistry, developmental anatomy, nutrition, anthropometry, clinical psychology, anthropology, psychiatry, genetics and experimental and comparative psychology.

The study of child development therefore has become a protean kind of postnatal embryology, a focal field for psychobiologic and medical knowledge, converging on the central problem of early human growth or development.[1] This is, of course, a prodigiously inclusive field of inquiry, but it is a legitimate one, because the phenomena of growth are subject to general and unitary laws which can be formulated only by coordinated contribution from several scientific domains. Growth is itself a unifying concept which depolarizes undue distinctions between mind and body, between heredity and environment, between health and disease. The more comprehensive investigation of child growth will inevitably bring developmental psychology and pediatrics into closer relation.

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* Submitted for publication, Jan. 18, 1929.

* Paper presented before The Section of Pediatrics of the New York Academy of Medicine, Dec. 13, 1928.

1. The terms "growth" and "development" may be used interchangeably. It is becoming increasingly difficult to maintain a distinction between growth as dimensional augmentation and development as differentiation.

PRINCIPLES UNDERLYING DEVELOPMENTAL DIAGNOSIS

Development, quite as much as disease, falls within the theory and the practice of pediatrics. Development may be studied from the standpoint of morphogenesis and of physical anthropology; it may also be studied from the standpoint of function, of behavior. The physiology of human development cannot be investigated or understood apart from behavior. In this sense the pediatrist has a vested interest in the whole problem of infant behavior. In this sense, also, I may hope to show that the elusive problem of mental growth can be approached objectively and tangibly through a systematic study of the behavior characteristics of normal and of abnormal infants. Before presenting concrete data from clinical and genetic studies, I shall summarize, in an introductory way, a few of the general principles which underlie the theory of a developmental diagnosis of infant behavior.

Behavior is at once the most integrated and the most inclusive expression of developmental status. At every stage of the organism it is the historical end-product of the life career of that organism. Therefore, behavior becomes a lawful index of developmental maturity.

Human behavior always tends to fall into ordered pattern.. Even the "random" behavior of the young infant is obedient to pattern. Although subject to individual variation and inflection, behavior patterns tend toward typical configurations which are characteristic of species and of age. These patterns are directly determined by the neural counterparts of both central and autonomic nervous systems, and indirectly by biochemical control.

These neural counterparts are primarily the products of intrinsic, organic maturation rather than of extrinsic influences. Being intrinsically determined, the neural counterparts strongly tend to follow the time ordered sequence of the life cycle. They are governed by age and by the inherent necessities of sheer developmental mechanics.

It takes time to grow. Development is profoundly conditioned by duration. Although it cannot be said that development is caused by the clock or the almanac, one may insist that development is a function of age, and that a recognition of the age values of behavior and of the behavior values of age constitutes the first essential for developmental diagnosis. The frequent failure to discern certain kinds and grades of mental deviation in early infancy may well arise from the fact that precise heed has not been paid to the factor of age in appraising the young infant. Age is so precisely potent in its influence that the age of the infant must be reckoned from the zero of conception. It is because development is so definitely conditioned by age and by lawful genetic sequences that developmental diagnosis and, in a measure, even developmental prediction become possible.

Behavior patterns yield to quantitative study, to systematic inventory and to detailed specification. Such specification, whether on an absolute or a graded serial basis, furnishes the orientational norms which are necessary for the measurement and for the early diagnosis of developmental defects and deviations.

NORMS OF BEHAVIOR DEVELOPMENT

It is to this task of normative formulation of behavior patterns that the research program of the Yale Psycho-Clinic is directed. The clinic, established in 1911, first confined itself to diagnostic and advisory work with children of school age; but the last ten years have been increasingly devoted to developmental research of the preschool period of childhood. Recently, a special grant of funds has made possible a concentration of this research on the first year of infancy.[2]

The normative research has been primarily concerned with normal children, but has been kept in close association with developmental studies of deviating and defective children referred to the service department of the clinic or examined in the New Haven Hospital and the Babies' Building of the Children's Community Center. In the first normative survey about 500 normal children were studied at ten ascending age levels: 1, 4, 6, 9, 12 and 18 months and 2, 3, 4 and years. Fifty children were individually examined at each age to determine the behavior items most distinctive of that age. Appropriate test situations were devised to bring out characteristic reactions in four fields: (1) motor coordination (posture, locomotion and prehension); (2) language (vocalization, speech and comprehension); (3) adaptive behavior (insight, intelligence and combining activity); (4) personal-social behavior (learning and habit formation and play activities). The frequencies of characteristic forms of behavior were calculated. The results were codified into a set of ten developmental schedules containing in all 150 classified behavior items.[3]

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2. The present staff includes two clinical examiners and research associates in anthropometry, experimental psychology and pediatrics. The clinic is housed in a residential type of building, with facilities for daytime care of infants, examining and observation rooms, a photographic laboratory and a guidance nursery. The guidance nursery is an adjunct to the service department of the clinic and is used for individual guidance work with children of preschool age and their parents.

3. Details concerning the norms and procedures in Gesell, Arnold: The Mental Growth of the Preschool Child: A Psychological Outline of Normal Development from Birth to the Sixth Year, including a System of Developmental Diagnosis, New York, The Macmillan Company, 1925, p. 447; Infancy and Human Growth, New York, The Macmillan Company, 1928, p. 418. A few of the illustrations and the table which follow are reproduced from the latter publication.

By means of these schedules it is possible to make an analytic, descriptive record of developmental status, and to estimate the maturity level of a child in the various fields of behavior. When applied with clinical caution, the schedules become norms for expressing and defining a developmental diagnosis. A similar preliminary system of schedules has been drawn up to cover the monthly increments of development during the first year of life. These graded schedules comprise 120 behavior items.

There are no peculiar difficulties in securing behavior responses from the young child. His very naiveté makes him a favorable psychologic subject. The materials used in a developmental examination are relatively simple, and include such familiar objects as spoon, cup, crayon, paper, pellet, string and 1-inch red cubical building blocks. These objects when presented under controlled conditions, in standardized situations, elicit characteristic responses, that is, distinctive behavior patterns which tend true to type and therefore have diagnostic significance. Take the reactions to the little red blocks, for convenient illustration. The 4 months old infant gazes at a block placed before him, but fails to pick it up; the 6 months old infant seizes the block with executive directness and puts it to the mouth; the 9 months infant bangs it against a cup in combining play; the 1 year old subject unwraps it from a paper covering; the 18 months infant stands on his own feet and builds a tower of blocks; the 2 year old assembles a row of blocks with deftness; the 3 year old builds a bridge of three blocks; the 4 year old, a more difficult gate, and the 5 year old reproduces from memory a complicated stairway model of ten blocks.

This progressive gradation in the child's reactions to the small red blocks shows how the patterns of his performance tend to keep lawful step with the maturity of his nervous system. Closely scrutinized and critically interpreted in relation to age norms, the behavior with the cube furnishes a substantial quota of objective evidence for estimating developmental status. An incisive summary of what a retarded child can and cannot do with ten building blocks may supply an index to his neuromuscular equipment. Indeed, if a 3 year old child can pile three blocks one on the other to make a tower, but cannot even with demonstration rearrange these three blocks to make a bridge (one block surmounting two), this item in itself might be suggestive of serious mental deficiency.

If this application of behavior norms is valid in principle, it follows that a refinement and improvement of such norms can carry one far beyond the detection of mental defect, and lead to the early diagnosis of numerous individual differences indicative of health and development of infancy. If the supervision of development is to become truly pre-

ventive, the technics of developmental diagnosis must be pushed into this period of early infancy.

NORMATIVE SPECIFICATIONS OF INFANT BEHAVIOR PATTERN

Mental growth proceeds so swiftly in the early sector of the life cycle that normative and diagnostic criteria must pay respect to small units of duration. The younger the organism, the more potent is any given unit of time in the economy of its development. In the normative research at the Yale Psycho-Clinic it has been found necessary to adopt the lunar month as the basic chronologic unit, the solar month being too variable

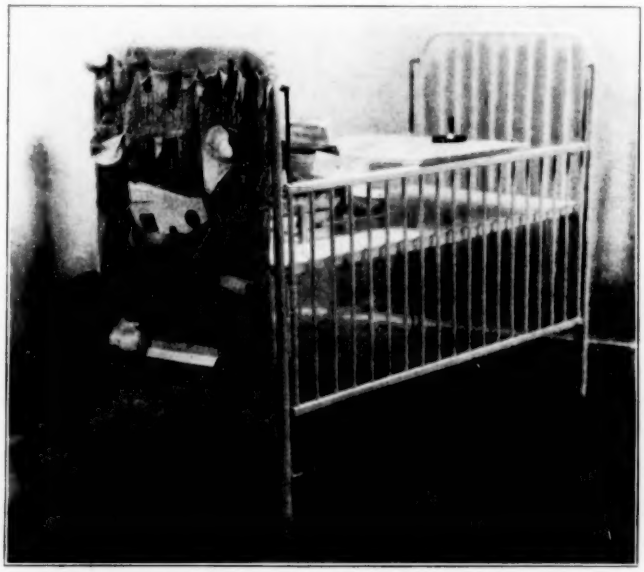

Fig. 1.—Clinical crib used for making developmental behavior examinations of infants.

for quantitative and statistical work. Beginning with birth, the first year of life has been blocked into fifteen age levels (in weeks 0, 4, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52). By means of such finer calibration, it should be possible to measure more closely the developmental characteristics of the infant.

A carefully selected, small group of normal infants is being intensively studied at each of these age levels. Ordinarily the mother and infant spend a half day at the clinic, and the observations are made, so far as possible, under optimum and controlled conditions. The methods of observation employed can be briefly indicated with the aid of the accompanying illustrations (figs. 1 to 8).

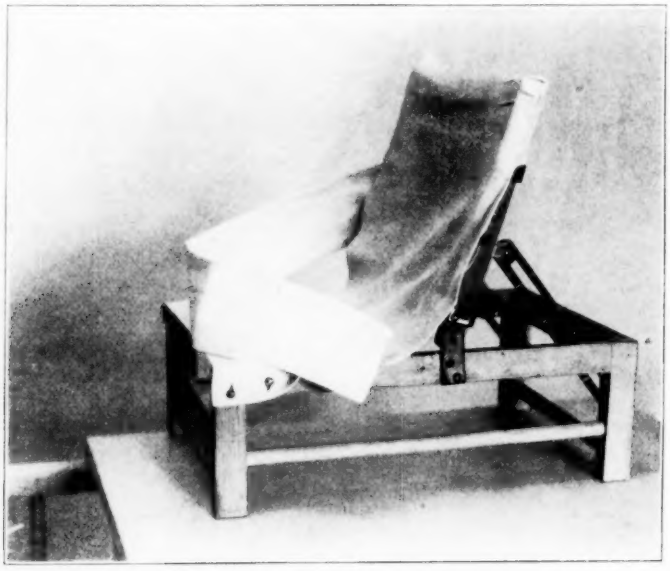

Fig. 2.—Detail showing infant's chair used in clinical crib set-up.

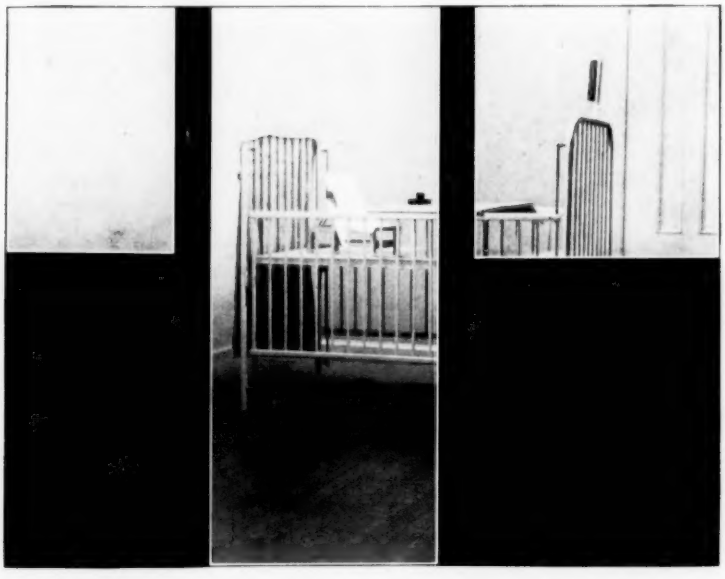

Fig. 3. —Examining room equipped with one-way vision screen to conceal observers.

The clinical crib (fig. 1) has been devised to standardize the test situations. It is built like an ordinary nursery crib, but has many adjustable features, which permit the platform and panels to be raised to variable heights. The side rails support a movable table top on which the test materials are put with careful regard for placement and details of presentation. When not in use, these materials are concealed in the pockets of the container bag hung at the rear end of the crib. This bag is removable and facilitates sterilization of the materials.

The infant supportive chair (fig. 2) is built along Morris lines and is provided with a removable canvas back and seat and abdominal belt; it supplies comfortable support for infants with imperfect sedentary

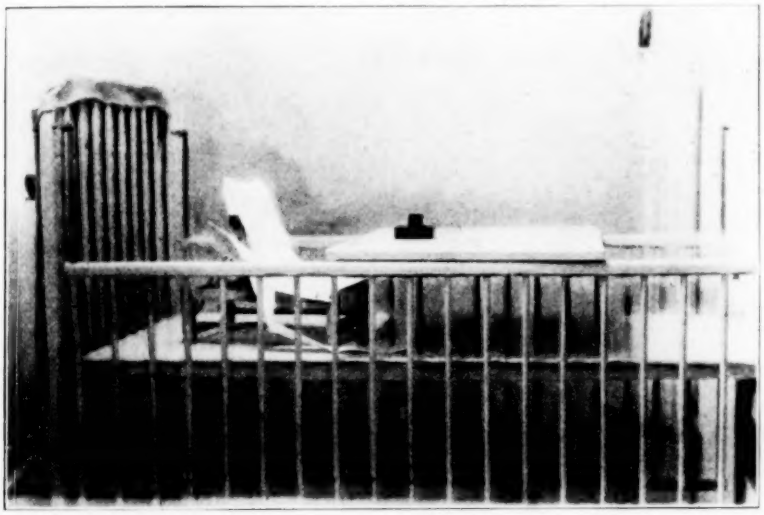

Fig. 4.—Photograph of clinical crib taken through the one-way vision screen showing its transparency.

postural control. Its sanitary and adjustable features have made it very serviceable.

To secure control of infant behavior observation, it is necessary to remove the distraction of complicating adults, whether parents, recorder or other assistants. And yet one wishes to permit the mother to view the examination. This difficulty has been effectively met by a specially devised one-way vision screen (figs. 3 and 4) which conceals the observer but not the observed. A folding panel arrangement of this screen is partly pictured in the illustration. In the actual set-up, the screen is a full length partition, which separates the observers who are stationed in a darkened alcove. The illuminated surface of the screen is painted white, with highly reflective enamel); the dark surface is

unpainted. The screen functions as a visual sieve, permitting one way vision only, a useful cloak of invisibility.

The photographic observation dome (fig. 5), an hemispherical structure, 12 feet in diameter, is located in the photographic laboratory of the clinic. It is in a sense the reverse of its astronomic prototype. The route of observation is inward; the operator, observers and parent are stationed without, segregated by the one-way vision screen which encases the dome. The interior is illuminated with a soft artificial light, so suffused that it offers no distraction to the infant in the clinical crib within.

Fig. 5.—Photographic observation dome with cameras mounted on two quadrants. The infant is within the dome; the operator and observers are outside the dome, concealed by the one-way vision screen encasing dome.

Instantaneous cameras under electrical control and a motion picture camera are poised on two quadrants at right angles to each other. The cameras may be placed in any position from horizon to zenith, and are operated by an electric switch, singly or simultaneously (fig. 6). Simultaneous pictures give control of the third dimension; direct overhead pictures yield valuable configurational data; the cinema records at once the spatial and temporal patterns of behavior.

With this equipment, it is possible to undertake somewhat systematically a charting of the development of patterns of behavior. The standardization of focal distances, and of illumination combined with the control of the experimental and age conditions serve to bring the

lines of growth into genetic sequence, so that different stages of maturity in the same child or in different children can be brought into organic comparison. When the cinema records, with 16 frames per second, are subjected to frame by frame analysis, they yield minute detail concerning the dynamics of any given behavior.

Figure 7 brings into composite view characteristic moments of behavior in one infant who was photographed in the dome at lunar month intervals. Space forbids comment on the individual pictures; but it can be readily seen from inspection that such records can assist in setting up definite criteria of performance for the interpretation of behavior growth. The pictures in the top row (1 week, 6 weeks, 8 weeks, 12 weeks), for example, show clearly both persistence and change in the pattern of the tonic neck reflex at four successive age levels.

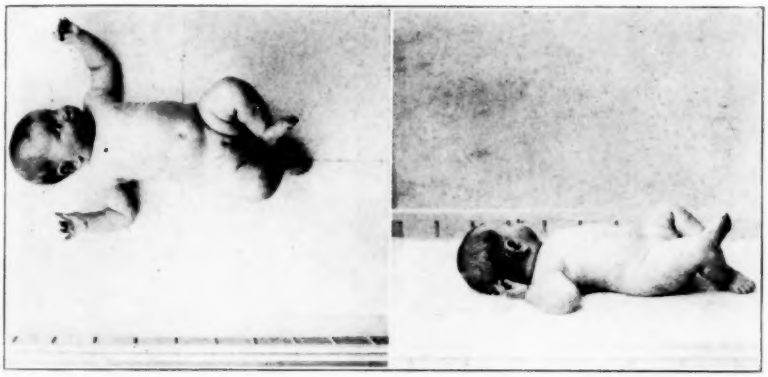

Fig. 6.—A pair of simultaneous photographs taken with one camera at the zenith and the other at the horizon of the photographic dome, showing spontaneous dorsal attitude of the infant.

Figure 8 epitomizes photographically the progressive changes in eye-hand reactions which mark the growth of prehension. The prehensory responses are elicited by placing a round pellet, 5 mm. in diameter, on the table surface, immediately in front of the seated infant. The typical reactions which occur may be recapitulated in the following, which is a genetic order: (*a*) no visual regard for small pellet, but fixation on a 1 inch sphere (16 weeks); (*b*) transient regard for the pellet; (*c*) more protracted visual fixation on the pellet with slight postural changes (20 weeks); (*d*) visual fixation with crude bilateral or unilateral approach; (*e*) unilateral, pronated approach with scratching in the vicinity of the pellet (24 weeks); (*f*) pronated hand approach with raking flexion resulting in occasional palmar prehension (28 weeks); (*g*) pronated hand approach with extension of index finger

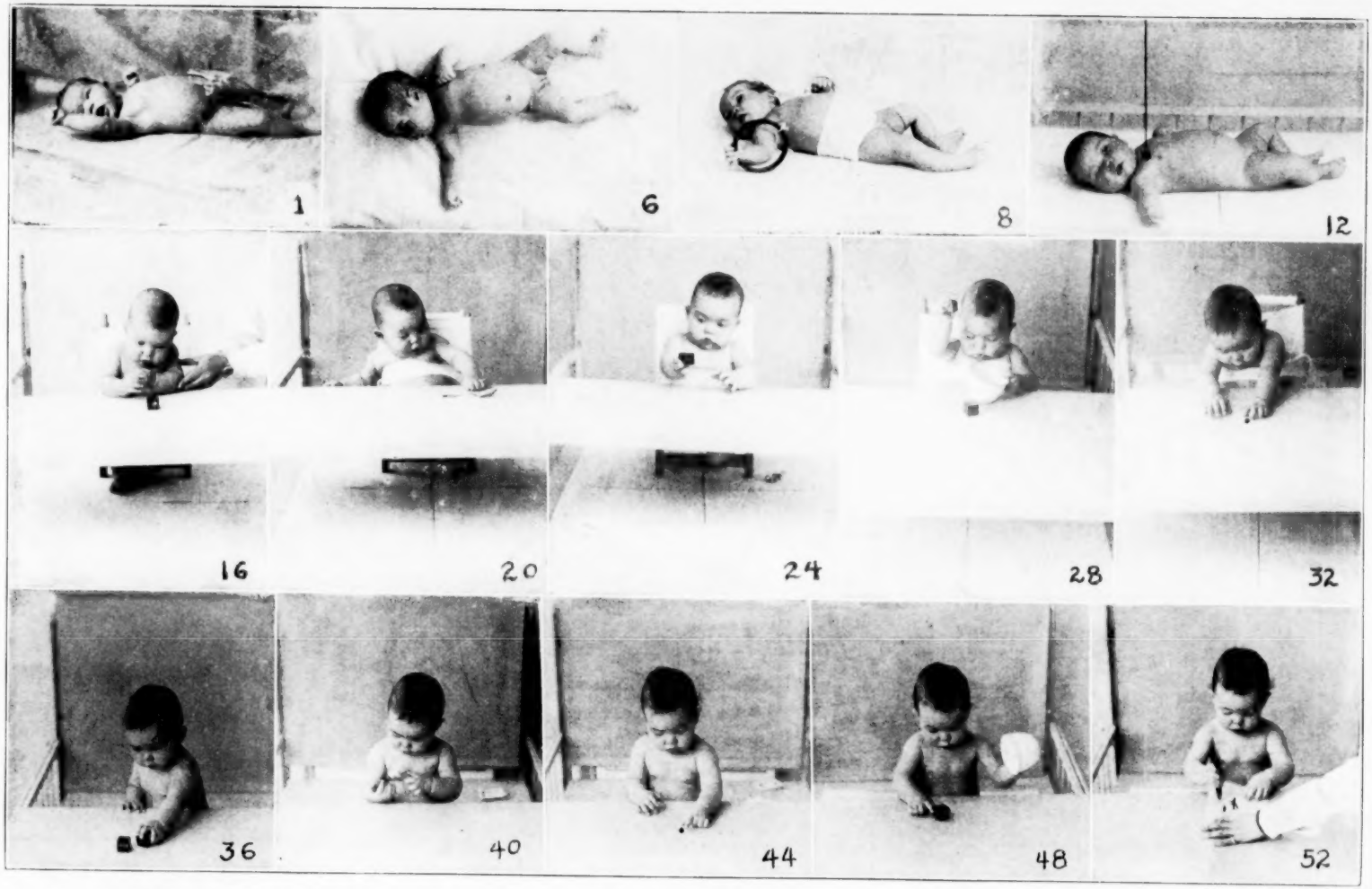

Fig. 7.—Developmental series of action photograph of one infant at the following ages: 1 week, spontaneous dorsal position showing tonic neck reflex; 6 weeks, more advanced dorsal posture with tonic neck reflex; 8 weeks, reflex clasp of ring without visual fixation (tonic neck reflex); 12 weeks, visual fixation on small dangling ball (tonic neck reflex); 16 weeks, visual fixation on cube; 20 weeks, visual fixation on spoon with postural response; 24 weeks, prehension of cube; 28 weeks, banging of cube; 32 weeks, raking attack on pellet; 36 weeks, pursuit of second cube; 40 weeks, inspection of bell; 44 weeks, precise pincer prehension of pellet; 48 weeks, transfer of cube, supported under arm; 52 weeks, spontaneous

and partial supression of other digits, resulting in poking or prehension by thumb in partial opposition to index finger (32 weeks); (*h*) rotation of wrist with pincer-like prehension by index finger and thumb (40 weeks); (*i*) perfection and further delimitation of pincer-like prehension (52 weeks). The ages given in parenthesis are shown in the photographs.

The last picture in the prehension series portrays a pair of retarded, identical twins (38 weeks old) at the moment of approach on the pellet. The striking resemblance of their behavior patterns in the pellet situation, observed at twelve periodic examinations between the ages of 4 months and 18 months, was most impressive. Such correspondence of performance denotes strongly that the sequence and character of many

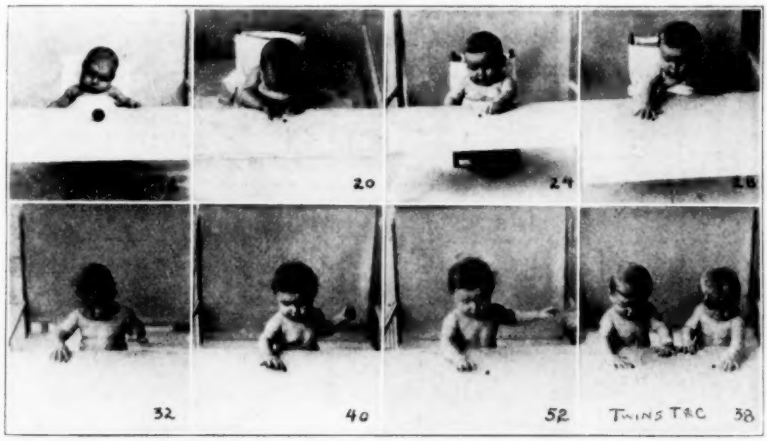

Fig. 8.—Developmental series showing growth of pellet prehension patterns at 16, 20, 24, 28, 32, 40 and 52 weeks. The picture in the lower right-hand corner shows identity of pellet prehension patterns in a pair of remarkably identical twins slightly retarded, at the age of 38 weeks.

behavior values are lawfully ordered by maturational factors which determine the basic trend and tempo of development.

CLINICAL STUDIES OF MENTAL GROWTH

It is this lawfulness of developmental mechanics which permits a quantitative approach to clinical problems of individual growth. To be sure there is no absolute unit of measurement for this growth; but there are objective norms, and sensible, comparative values, which enable one to plot approximately the levels of maturity for specific fields of behavior or for the individual as a whole. It is convenient to express these levels in ages; for every age has its characteristic behavior values, and conversely behavior capacities have a normative

age value. Graphically, the normal course of development may be represented by a logarithmic type of curve, which suggests early rapidity of growth and later deceleration. Such an ideal average curve is made the standard of reference in the accompanying growth graphs.

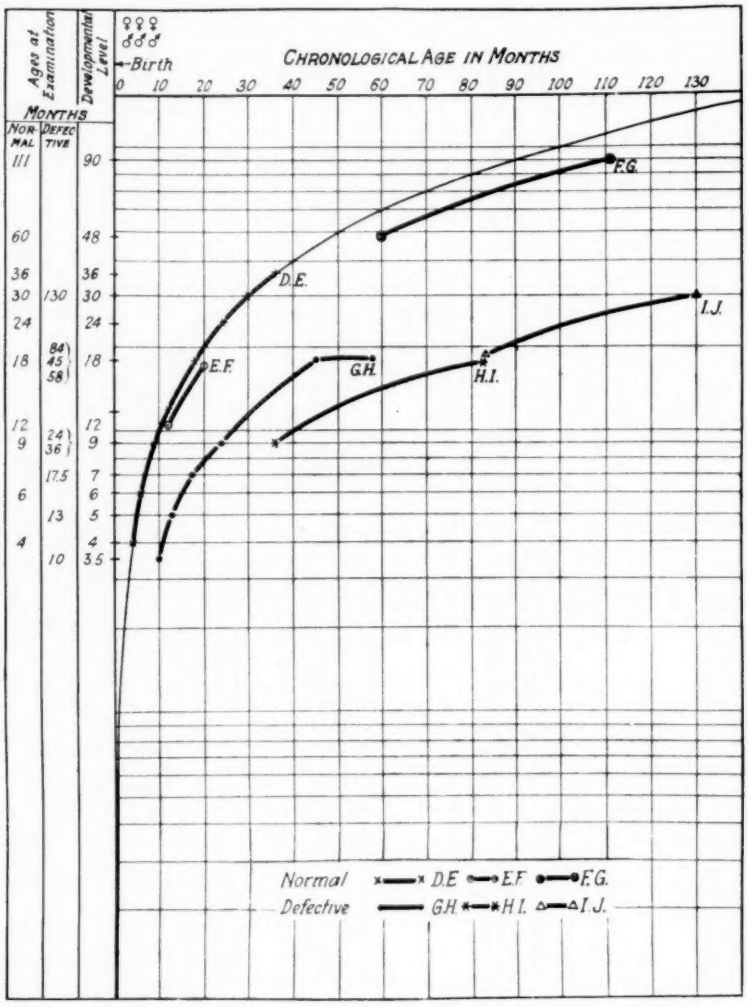

Fig. 9.—Mental graph of six siblings; three normal, three defective.

These graphs are reproduced here, with only slight comment, to illustrate the possibility of genetic studies of developmental conditions which lie definitely within the field of clinical pediatrics, to say nothing of the implications for the broader field of preventive pediatrics.

Figure 9 is a graph assembling six individual mental growth curves. Three of the children are definitely normal and have pursued a similar

course of early development; the other three have pursued a definitely subnormal course.

Figure 10 is a combined graph which shows the mental growth and status of thirty mongols, from 4 to 150 months of age, referred to

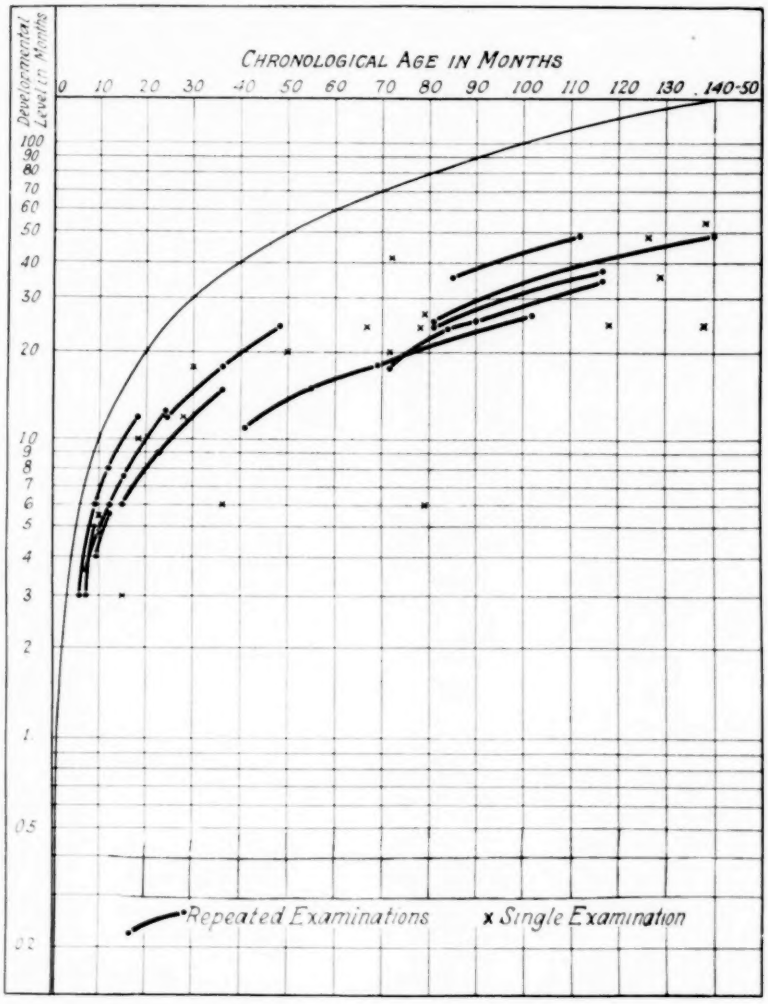

Fig. 10.—Graph showing mental growth and status of thirty mongols.

the clinic. The clustering of the curves in one segment of the graph is evident.

Figure 11 is the growth curve of a child who suffered from marked malnutrition during the first year of infancy, but who has shown consistent acceleration of mental development up to his present age (4 years).

Figure 12 is a graph showing an atypical course of development in a case of dystrophy, with progressive deterioration and marked stereotypy of behavior.

Figure 13 pictures the development of a pronounced case of puberty praecox, in which menstruation began at 3½ years. The menstruation has been regular since the age of 4. In spite of a full decade of precocity in physiologic maturity, the course of mental growth has remained remarkably stable and surprisingly near an average course. The nor-

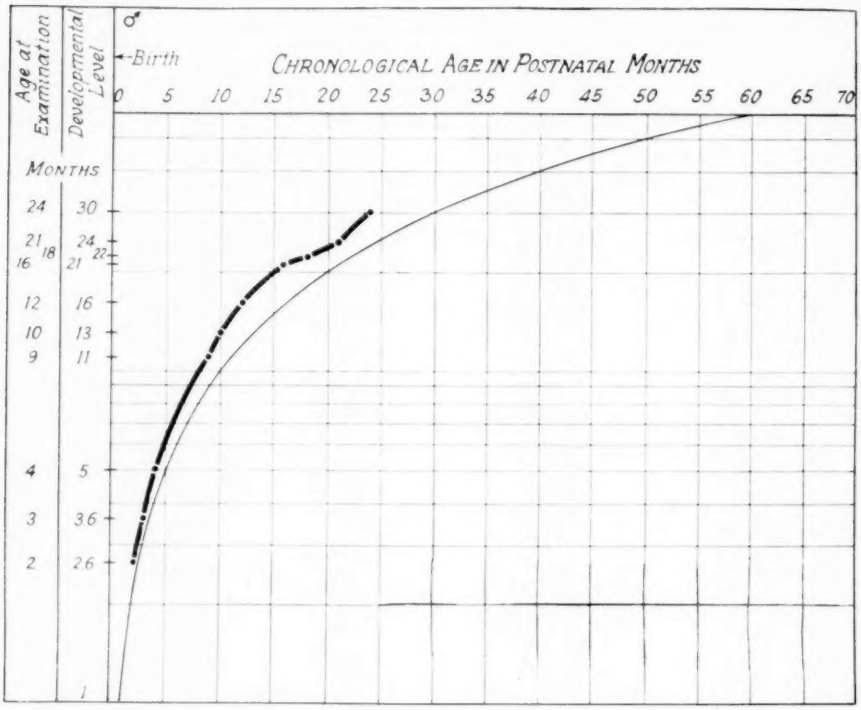

Fig. 11.—Graph of mental growth showing sustained acceleration from early infancy.

mal maturation of the nervous system is, to a considerable and significant degree, undisturbed by many adverse and unusual conditions.

Figure 14 is an analytic growth and age chart of J. L., born two months prematurely. It brings out the significant fact that the behavior development of the healthy premature infant tends to remain true to an ordinary course. A long series of examinations shows that the behavior patterns mature in relatively normal sequence, when the chronological age factor is corrected by discounting the prematurity. A premature postnatal environment or a protracted uterine environment is

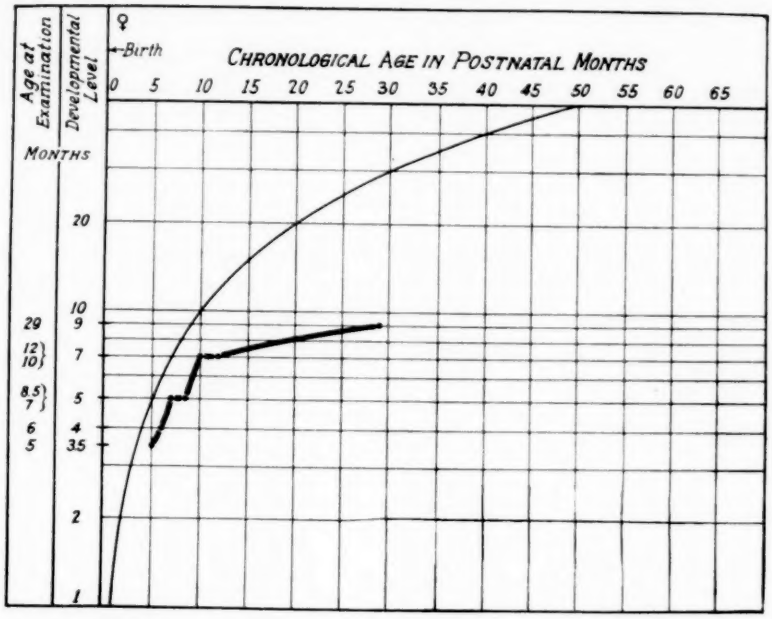

Fig. 12.—Mental growth graph showing atypical course of development in a case of dystrophy.

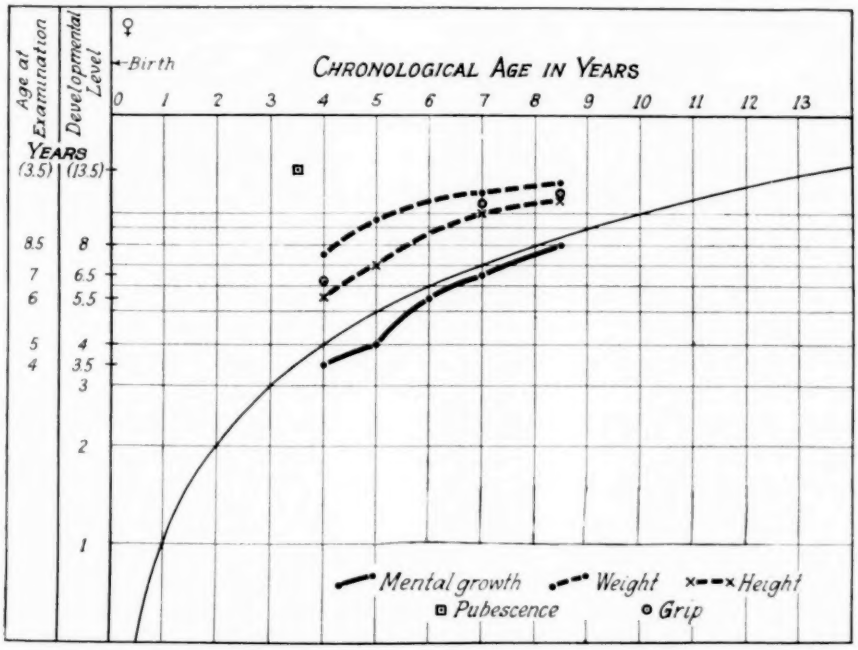

Fig. 13.—Showing precocious physical development with consistent low average mental growth in a case of puberty praecox.

not in itself competent to impose a marked deviation on the order of emergence or the form of the behavior patterns. The maturational factors retain their potency, unless they suffer actual damage from the complications of premature or postmature birth.

The accompanying table assembles the approximate developmental ratings of J. L. (two months premature). This table expresses in round figures the interesting relations between age and maturity level which came to light in a detailed study of the development of behavior patterns in a premature infant.

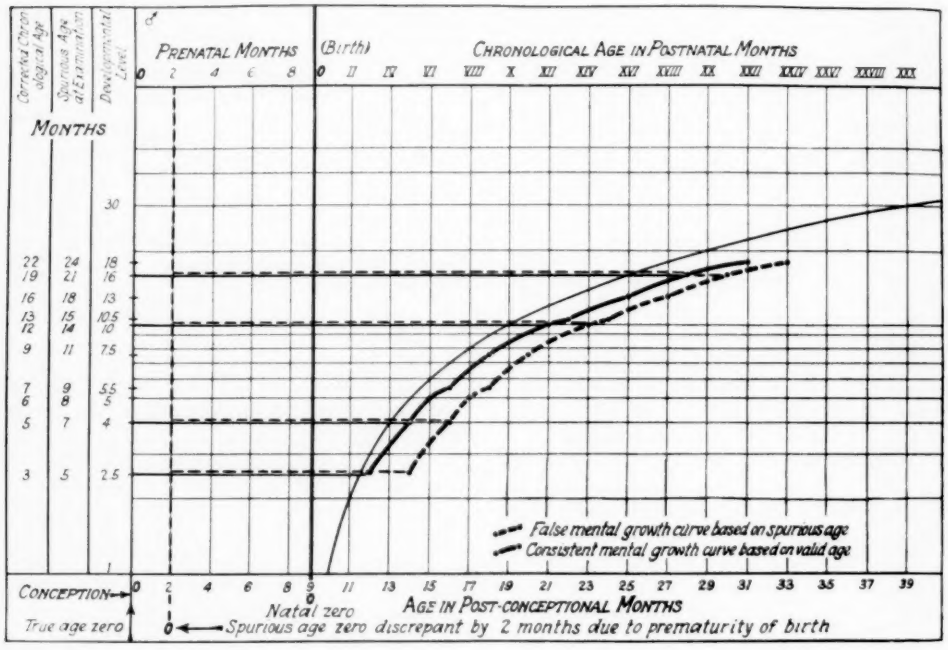
Prenatal Months
(Birth)
Chronological Age in Postnatal Months
Months
False mental growth curve based on spurious age
Consistent mental growth curve based on valid age
Conception
True age zero
Natal zero
Age in Post-conceptional Months
Spurious age zero discrepant by 2 months due to prematurity of birth

Fig. 14.—Analytic growth and age chart of an infant born two months prematurely.

These normative and growth studies have been sketchily presented to indicate the feasibility of diagnosing individual differences of development through systematic study of behavior. Behavior is not an elusive will-o'-the wisp. It expresses itself in patterns which can be clinically perceived and quantitatively stated. Development is so lawfully conditioned that in spite of its intricacy it will yield to the investigatory methods of medical science. The maturational determiners of the growth of the nervous system, although not immutable, are so stably and regularly entrenched, that the developmental status of the individual can always be interpreted in terms of ascertainable norms of maturity.

But the application of norms of behavior is not restricted to the diagnosis of maturity status in a specific sense. Behavior is also a subtle and sensitive index of physiologic status. Accordingly, behavior signs become an integral part of medical symptomatology, and behavior norms become the criteria for discovering and for supervising conditions of health and disease in infancy.

This brings one to a consideration of some of the possibilities of the diagnosis of behavior in relation to child hygiene and clinical pediatrics. These possibilities may be discussed with reference to (1) the organization of developmental supervision; (2) pediatric research of behavior symptomatology; (3) medical education in the behavior aspects of pediatrics.

Developmental Ratings of J. L., Born Two Months Prematurely

Order of Examination	(a) Postnatal Chronological Age, Months	(b) Conceptional Age, Months	(c) Developmental Age, Months	(d) Corrected Chronological Age, Months	(e) Genetic Age Level = e + 9 Mo.	Genetic Quotient e / b	Spurious Developmental Quotient e / a	Corrected Developmental Quotient e / d	Clinical Prediction BN, Borderline Normal
1	5	12	2.5	3	11.5	96	50	83	?
2	7	14	4	5	13	93	57	80	BN
3	8	15	5	6	14	93	62	83	BN
4	9	16	5.5	7	14.5	91	61	80	BN
5	11	18	7.5	9	16.5	92	68	83	BN
6	14	21	10	12	19	90	71	83	BN
7	15	22	10.5	13	19.5	89	70	80	BN
8	18	25	13	16	22	88	72	81	BN
9	21	28	16	19	25	89	76	84	BN
10	24	31	18	22	27	87	75	82	BN
x	5 yr.	5 yr. 7 mo.	4 yr.	4 yr. 10 mo.	4.75 yr.	85	80	83	

POSSIBILITIES OF DIAGNOSIS OF BEHAVIOR IN RELATION TO CHILD HYGIENE AND PEDIATRICS

The Organization of Developmental Supervision.—The supervision of nutrition in infancy is, and will doubtless remain, the central concern of pediatrics, and here the pediatrician maintains a balanced interest in disease and in normal growth. His attitude and his technic in this field constitutes perhaps the most tangible advance which has been made on a large scale in preventive medicine. The problem of nutrition is so fundamental that by implication, and often by actual exigency, it includes the psychologic and functional aspects of the individual growth. The protection of the nutritional health of the child thus becomes the natural stage for a broader and equally continuous type of developmental supervision. The technic of this developmental supervision will be slowly evolved, but it will come to include the mental as well as the bodily economy of the child's total growth. It will include his behavior patterns and his behavior trends, for they are part and parcel of his entire, indivisible growth.

Although at first glance this seems like an expansive and abstract concept of the province of pediatrics, such an extension of scope is almost inevitable if pediatrics continues its present position as a regional specialty converging the resources of general medicine and biology upon infancy. The whole tendency of modern science, because of its increasing diversity and intricacy, is toward organismal concepts which stress and preserve the unity of the individual. Among the biologic sciences, there is an increasing hyphenation of contiguous disciplines which reflects this tendency. Embryology is becoming physiology; the physiology of development is incorporating basic problems of behavior; anatomists are making experimental researches of immediate importance to psychology. The complexity of this whole situation, regarded from the standpoint of clinical science and of preventive medicine, places an increasing premium on investigatory and professional integration. The status of pediatrics as a correlating nucleus of general medicine becomes reinforced. It is impossible to see how pediatrics can avoid a fundamental reckoning with the problems of human behavior.

A large part of the work of the practicing pediatrician is already concerned with relatively normal infants, not suffering from acute illness, but presenting problems of hygiene, of posture, of habit formation, of behavior deviation and of behavior disorder. Even in the field of nutrition he is not perplexed so much by dietary requirements as by such "psychologic" phenomena as loss of appetite, food intolerance, faulty feeding habits and the conspiring influences of the child's total behavior day and of the family situation. Indeed, infant hygiene cannot be reduced to purely physical terms. In the final analysis, many of the primary factors of feeding, sleeping, exercise, rest, energy and metabolism reduce themselves to forms of behavior, subject to laws of habit training and of emotional conditioning. Basically, these problems of infant hygiene find an ultimate reference in the personality of the infant and in the infant-parent relationship.

For every age group and for every individual there are, therefore, ascertainable "norms" of behavior which must enter into an estimate of his mental and physical health. Any full inquiry into his health status must give systematic heed to these behavior conditions and bring them into the scheme of developmental supervision.

Periodic health examinations will then become developmental inventories, and the child's behavior assets and liabilities will be entered into a continuing, biographic record. Each examination is a check on another. The physician becomes an advisor with respect to the child's behavior health even during the first year of infancy, and takes a preventive interest in symptoms of mental welfare. The more complex and exacting problems of mental diagnosis and treatment will naturally be referred to the psychiatrist; but the problems of mental hygiene are

too numerous and too ubiquitous to be assigned to any specialty. The child's hygiene, at least, remains indivisible.

It is not assumed that every pediatrician will become an expert in mental medicine. Neither, however, can it be assumed that the vast field of developmental hygiene should be undertaken by an additional and supplementary mental service. Applied forms of educational psychology are penetrating into the preschool levels of childhood, and they have important contributions to make. It is inconceivable, however, that society will permit ambitious programs of infant training and infant conditioning, apart from the safeguards, the technic and the mores of medicine. Looking well into the future, the responsibility and the participation of pediatrics in a progressive organization of developmental supervision seem established.

Pediatric Research of Behavior Symptomatology.—One assumption is made throughout this discussion; namely, that growth is a valid scientific concept which falls within the scope of preventive medicine, and that development and disease are inextricably related concepts. Maldevelopment is frequently an expression of disease, and, conversely, diseases are constantly reflected in deviations of development. Clinical anthropology and physical diagnosis supply many keys to this profound interrelation, but behavior is probably the master key.

For this reason, the scientific study of infant behavior from the standpoint of symptomatology becomes an important phase of preventive pediatrics. In spite of its ordered stability, the growth complex is to an undetermined degree, alterable. To affect these alterations, the behavior signs of significant deviations must be sought and found early.

Departures from general health and from optimum nutrition, the onset of disease, the course of illness and of convalescence all tend to express themselves by more or less distinctive behavior signs. The skilled clinician is aware of a host of them. He utilizes his knowledge in his judgments of diagnosis, of prognosis and of treatment. Scattered, casual references to such behavior signs abound in a study of cases reported in the literature. It can scarcely be said, however, that behavior symptomatology has attained a systematic status in clinical pediatrics. At any rate, there appears to be abundant opportunity for a behavioristic type of clinical investigation.

Behavior symptoms figure in every syndrome. Diseases do not only have pathologic entity in the anatomic and physiologic sense; they have pathologic entity in the sphere of behavior. Behavior signs, which are correlated with the peculiarities of prodromal, active and resolving phases of disease processes, would yield to exploration. The field is one of importance and great fertility. It would undoubtedly serve the advancement of clinical pediatrics if systematic behavior studies were

more frequently undertaken at hospitals where selected cases are under extended observation and treatment. Many of these cases now scientifically wasted provide an almost experimental etiology for the elucidation of laws of child development. Harvey's observation still holds: "Nature is nowhere accustomed more openly to display her secret mysteries than when she shows traces of her workings apart from the beaten path."

The modern children's hospital with facilities for research is in a position to incorporate the investigation of behavior symptomatology into its programs. In the field of treatment and in the methods of child care there are permanent opportunities for the study of procedure from the psychologic standpoint of behavior control. Incidentally, there are many aspects of management of both the hospital ward and the individual patient that are essentially psychologic and that call for a more discriminating recognition of the behavior equipment and the behavior requirements of children.

From the standpoint of the hospital one may also raise the question whether the behavior characteristics of the infant should not find a more definite place in the case records. By means of simple bedside tests it would be possible to secure a brief inventory of behavior items, which would carry well beyond the scope of the standard neurologic reflexes. When such behavior inventories are adopted as a matter of routine and are given a status in the case histories, they will inevitably prove their value both for research and for clinical medicine.

In summary, behavior is more than a byproduct in the clinical study of problems of infant development. Behavior is not, in any restrictive sense, the subject matter of a separate scientific or medical discipline. Behavior, in the psychobiologic sense of the term, is an organic manifestation of complexes of growth and of disease, and therefore an essential factor in the interpretation of those complexes.

Medical Education in the Behavior Aspects of Pediatrics.—Periodic health examinations and a periodic normative survey of behavior patterns can be brought into association in a supervisory type of developmental pediatrics directed toward the early recognition and more timely control of growth conditions. The demand for this type of pediatrics is becoming clearer, both in the fields of private practice and of public health. Systematic health supervision is only in its beginning, but in principle a revolutionary increase in medical and social control has already been achieved. How this supervisory service in infant and mental hygiene will actually be organized no one can, of course, predict. The methods of developmental pediatrics will naturally take shape slowly, but probably with the same steady and sound growth which has marked the advances of preventive pediatrics in the supervision of infant nutrition.

Research in child development and research in the behavior aspects of pediatric problems will contribute to the definition of diagnostic and supervisory technic. But almost equally important are forms of medical education, both preprofessional and post-graduate, which will emphasize the psychologic or the psychobiologic aspects of individual development. Toward this end, curriculum and clinical training alike will have to deal more systematically with the characteristics of the normal infant and with the norms of typical, optimum mental development. This will entail fundamental attention to the developmental aspects of child psychology and to the genetic aspects of neuropsychiatry. The multiplication of special courses and lectures in adult psychiatry, mental hygiene and psychopathology can scarcely meet the situation. Purely supplementary instruction in these fields might even operate to retard the desired correlation of mental and physical hygiene. What is most needed is a developmental approach which will focus on the central concept of growth from the outset, and which will bring health and abnormality in both psychical and physical spheres into organic relation. Only in this way can the psychologic outlook be assimilated into the biologic point of view of the medical student, and only in this way likewise can a scientific outlook of mental hygiene become assimilated into the attitude of the physician.

I appreciate that I have dealt with broad and highly complicated problems in a somewhat general way. It is probable, however, that I have not overemphasized the significance of the strategic position of pediatrics in the medical and social scheme. It seems certain that the preventive methods of pediatrics contain a germ capable of endless development in the supervision and control of early human growth.

ROBERT PEMELL
?-1653

JOHN RUHRÄH, M.D.
BALTIMORE

Among the all but forgotten writers on pediatrics is Robert Pemell, a practitioner at Cranebrooke, in the county of Kent. Had it not been that he possessed a love of setting down in writing his observations and studies, he would have remained forever unknown, but he did write five books. His first venture into medical literature was entitled, "De morbis capitis" or "The Chief Internal Diseases of the Head." This little volume was written in English, for Pemell was among the first to write in the common tongue, but he rather proudly gives evidence of his learning by his numerous references and quotations. The book has at the beginning a poem in Latin with an English translation by John Elmerston, School-Master of Cranebrook. Doubtless this poem was a sort of payment for treatment or advice. It ends:

> Who likewise hath us of choice Medicines told,
> For every Evill's cure, and due relief;
> Whatever larger Physick Volumes hold
> Good for thy head, is here compriz'd in brief.
> Let this good friend be thy Physitian
> Whose skilfull Counsell, and Direction,
> Shall either keep thy head in healthfull case;
> Or by his Art, away the Evill chase.

Pemell also wrote two books on simples and two on pediatrics. One of them, entitled "Help for the Poor," is a popular treatise on the prevention and cure of disease, which gives him a place among the early workers in public welfare. His book on children is entitled:

DE MORBIS PUERORUM
or,
A TREATISE
of
The Diseases of Children
With
Their Causes, Signs, Prognosticks, and Cures, for the benefit of such as do not understand the Latine Tongue, and very useful for all such as are House-keepers, and have Children.
With the Contents of several Chapters, as also an Alphabetical Table of all the Diseases mentioned herein.
By Robert Pemell Practitioner in Physick, at Cranebrooke in Kent,
May the 29, 1652,
LONDON
Printed by F. Legatt, for Philemon Stephens, at the guilded Lion in Pauls Church-yard, 1653

It is a small book of fifty-eight pages, divided into twenty-eight chapters as follows:

THE CONTENTS OF THE SEVERAL CHAPTERS

Of ulcers and sores in children's heads
Of Lice
Of the Scab and Itch
Of the falling Sicknesse and Convulsion
Of pain in the ears, with inflammation
Of breeding and coming of Teeth
Of inflammation of the mouth and throat, with ulcers and sores thereof
Of Feavers
Of the small Pox and Measles
Of watching out of measure and want of rest
Of fear, startling and terrible Dreams
Of Rheume, the cough, and shortnesse of breath
Of Vomiting, and weaknesse of the stomach
Of the Hicket
Of the Consumption, or leannesse, and of the Rickets
Of Gripings and fretings in the belly
Of Worms
Of Ruptures and Burstings
Of swelling, or coming forth of the Navel
Of inflammation of the Navel
Of the swelling of the Cods
Of falling of the Fundament
Of the stone, and difficulty of making water
Of Pissing in bed
Of the diseases called Saint Anthonies fire, or wilde fire, as also of burning and scalding
Of fretting, chafing, or galling of the skin in the groines

Pemell was not very original in his ideas, which were largely taken from other authors—a practice not at all confined to any age or place. He understood that improper or spoilt food caused diarrhea. He suggested enemas of mixtures which were more or less astringent and a number of applications to be made to the abdomen, which if they did not help did not hinder. Internally, he suggested the use of either syrup of roses solutive or honey of roses solutive, which had a constipating effect.

His therapeutic suggestions, when analyzed, are often sound. Thus, for ulcers and sores on children's heads he recommended washes, and if these were not effective he recommended making them with wine, i. e., dilute alcohol, the antiseptic action of which is well known. He used sulphur in ointments or litharge of silver. He also recommended "washing the head with soap suds made strong. If these ulcers eat to

De Morbis Puerorum,

OR, A

TREATISE

OF

The Diſeaſes of Children;

WITH

Their Cauſes, Signs, Prognoſticks, and Cures, for the benefit of ſuch as do not underſtand the Latine Tongue, and very uſeful for all ſuch as are Houſe-keepers, and have Children.

With the Contents of the ſeveral Chapters, as alſo an Alphabetical Table of all the Diſeaſes mentioned herein.

By *ROBERT PEMELL* Practitioner in *Phyſick*, at *Cranebrooke* in *Kent*. May the 29. 1653.

LONDON,

Printed by *J. Legatt*, for *Philemon Stephens*, at the guilded Lion in *Pauls* Church-yard. 1653.

the skul, then use hony of Roses mixed with a little spirit of Wine, and afterwards the powder Birthwort and natural Balsam."

For the most part he used simple and homely remedies, but following the fashion of his days and ours he occasionally recommended organotherapy quite as remarkable as that advised by many modern manufacturers.

One short extract must serve as an example of his style:

OF FRETTING, CHAFING, OR GALLING OF THE SKIN IN THE GROYNS

THE CAUSE

Children are much troubled with the skin going off in their groins and thighs; which is caused by reason of the sharpnesse of their urine, especially if they be not often changed with fresh linen.

THE SIGNS

The signs are apparent, for the skin is raw, and the child very unquiet therewith.

THE PROGNOSTIKS

This disease is not hard to cure, yet because it causeth pain, and brings watchings to the childe, if it be not taken in time it causeth ulceration in those parts

THE CURE

The Linnen of the child must be often changed, lest by the wetnesse thereof the disease be made worse. Wash the thighes and buttocks with Plantain water, with Rose, or Nightshade water, or make a decoction with Plantain, Shepheards-purse, Horsetail, and Knotgrasse, and bathe the place therewith. Or, anoint it with a little Capons grease, and lay a Linnen cloth to it: or anoint it with Pomatum, or strow on it the powder of a post, or any old wood that is wormeaten, or meal dust, or Bean flower; or else,

A POWDER

Take red Roses and Orris root, of each a quarter of an ounce; beat them into powder, and use it as before, by strowing it upon the raw place.

News and Comment

THE CHILDREN'S FUND OF MICHIGAN

Senator James Couzens, of Michigan, has created a $10,000,000 fund to promote the health, welfare, happiness and development of the children of Michigan and elsewhere in the world. The Children's Fund of Michigan, the corporation which will administer the fund, will be under the direction of Dr. Hugo Freund. The total of Senator Couzen's gifts to children amounts to $17,000,000.

NEW BABY HOSPITAL AT DALLAS

Plans have been perfected for the new baby hospital at Dallas, Texas, made possible by the gift of $130,000 by T. L. Bradford. The hospital will have an outpatient department in the basement and will be used exclusively for babies under 5 years of age. This hospital is the direct outgrowth of the Dallas Baby Camp, which developed under the guidance of Dr. Leslie Moore.

UNIVERSITY NEWS

Appointments and Promotions.—Dr. David H. Shelling was appointed instructor in pediatrics at the Johns Hopkins Medical School and assistant physician to the Harriet Lane Home for Sick Children of the Johns Hopkins Hospital, Baltimore.

Dr. John Foote, professor of diseases of children at Georgetown University School of Medicine, has been made dean of that school. Dr. Foote is well known in pediatric circles, for his work on the new-born, and for his knowledge of the history of pediatrics, especially of the child in medieval art. He is, aside from his medical duties, a trustee of the National Geographic Society.

PERSONAL

Prof. I. A. Abt of Chicago has been elected an honorary member of the Deutsche Gesellschaft für Kinderheilkunde.

SCHOOL FOR CRIPPLED CHILDREN

Dr. and Mrs. David W. Smouse of Los Angeles have given $250,000 for the erection of a specially equipped school for handicapped children in Des Moines, Iowa. An important object of the school will be to find the vocational possibility of each child, so that all may be taught a way to usefulness, and happiness.

Abstracts from Current Literature

Anatomy and Physiology

THE BONY LABYRINTH OF THE NEW-BORN AND OF THE ADULT: A COMPARATIVE STUDY. G. E. TREMBLE, Arch. Otolaryng. **9**:175 (Feb.) 1929.

An extensive comparative study was made of the ear of the new-born infant and the adult, the corrosion or metallic cast method being used. The internal ear, the tympanic cavity, with the auditory ossicles, and the mastoid antrum were found to be nearly identical in size in both the new-born infant and the adult, while the external auditory meatus, eustachian tube and mastoid portion of the temporal bone differed greatly. The spread and distribution of the mastoid cells are not attained until after puberty.

Tables showing the measurements obtained in the ears of both infants and adults are given.

BARNETT, Chicago.

RESPIRATORY FREQUENCY OF THE WELL CHILD. H. VOGT, Monatschr. f. Kinderh. **42**:460, 1929.

In a clinical study, the author found the respirations of the new-born infant to average thirty-six a minute. During the first year, they sink to from twenty to twenty-five. During sleep, both in infancy and in childhood, the rate is somewhat reduced.

GERSTLEY, Chicago.

Pathology, Bacteriology and Biochemistry

FURTHER OBSERVATIONS ON METADYSENTERY AND THE METADYSENTERY BACILLI, WITH REMARKS ON THE CLASSIFICATION OF BACTERIAL DYSENTERIES. ALDO CASTELLANI, J. Trop. Med. **31**:185 (Aug. 1) 1928.

This work is of value in enabling one to identify the various bacilli of dysentery. Particular attention is paid to the group of bacilli in metadysentery. The bacilli of this group may produce a chronic infection. The patient feels tired, nervous and depressed and has no appetite; he complains of flatulence with occasional attacks of simple diarrhea followed by long periods of constipation. The diagnosis is based on a thorough bacteriologic examination of the stool, and on the examination of the patient's blood for specific agglutinins.

LESLIE, Evanston.

INANITION FROM REDUCED DIET AND FROM DEFICIENT DIET. G. MOURIQUAND and A. LEULIER, Nourrisson **17**:16 (Jan.) 1929.

One group of guinea-pigs was fed a diet that was balanced but lacking in calories; a second group was fed the same diet without lemon juice (vitamin C).

The animals in group 1 lived from fifty to sixty days, losing in this period about 25 per cent of their original weight. They maintained a good appetite to the end. Those in group 2 showed a gradual loss of weight for from eight to ten days; then, synchronously with a marked anorexia, there occurred a sharp drop in weight and a marked anemia with other signs of scurvy. The average length of life in the second group was twenty days.

MCCLELLAND, Cleveland.

THE HEMATOPOIETIC ACTION OF BILIRUBIN AND OTHER HEMOGLOBIN DERIVATIVES. F. VERZAR and A. ZIH, Biochem. Ztschr. **205**:388 (Feb.) 1929.

The spleen and bone marrow extract used by the authors produced hematopoiesis in normal rabbits. The authors thought that some hemoglobin derivative

formed by the reticulo-endothelial cells might be the stimulating factor. For this reason, rabbits were fed from 0.5 to 3 mg. of bilirubin. This caused a transient increase in the red cells in from twenty-four to forty-eight hours. When larger amounts (from 5 to 25 mg.) were fed, the increase was followed in most cases by a marked decrease. The results with biliverdin, hemibilirubin and hematoporphyrin were not constant. Hemoglobin given by mouth in doses of from 0.5 to 25 mg. stimulated the production of red cells, but the doses of more than 12 mg. at times caused a decrease. In the most effective hematopoietic stimulant, liver extract, there are no blood or bile derivatives. The authors stated, however, that not all hematopoietic activity was due to the same stimulus.

BRAHDY, New York.

ANEMIA IN RATS AND LIVER TREATMENT. MARTHA ORBAN, Monatschr. f. Kinderh. **42**:402, 1929.

Rats which were made anemic by bleeding were given liver either as the powdered organ or the extract. The treatment had no effect. The author concludes that the effect of liver cannot be one of direct stimulation of the blood-making organs.

ALIMENTARY INTOXICATION AND PERMEABILITY OF THE MENINGES. S. ROSENBAUM, Monatschr. f. Kinderh. **42**:419, 1929.

In young dogs the effects of exsiccation and endotoxin poisoning, individually and combined, were studied with reference to increasing the permeability of the meninges to certain dyes. The reactions were different with different dyes. As a rule exsiccation proved more effective than endotoxin poisoning, but the combination of the two was much more effective than either alone. These experiments may explain the severe cerebral symptoms in alimentary intoxication.

GERSTLEY, Chicago.

THE BLOOD CATALYSIN IN VARIOUS DISEASES OF CHILDHOOD. K. P. SARILOWA, Pediatriya **12**:248, 1928.

Catalysin is a complex protein compound, the function of which is most probably that of strengthening the resistance of the organism to various infections. The author, using Bach's method, studied the catalysin of the blood in various diseases. The normal catalysin index varies between 14 and 18. The author's conclusions were that pathologic processes always decrease the catalysin index of the blood, the amount of decrease depending on many factors, such as the nutritional status of the patient, the degree of anemia and the status of the vegetative nervous system.

GASUL, Chicago.

Nutrition

THREE CASES OF RICKETS IN WHICH IRRADIATED ERGOSTEROL WAS USED. H. PRETET and M. KAPLAN, Bull. Soc. de pédiat. de Paris **26**:300 (June) 1928.

The patients were aged 20, 30 and 9 months, respectively. They were given 1:400 of irradiated ergosterol in olive oil, 15 drops, which was gradually increased to 40 drops, in milk, three times daily. They showed complete healing clinically and roentgenologically in from two to three months, but the phosphorus and calcium of the blood showed a slow increase to somewhat below the normal figures during that time. In the discussion, it was stated that the general condition, muscular hypotonicity and anemia which usually accompany rickets show a more marked improvement with cod liver oil than with irradiated ergosterol, and that the latter product is variable in its potency, and should always be standardized and dated.

BENJAMIN, Montreal.

CHOICE OF FEEDING IN HYPOTHREPSIA. A. B. MARFAN, Nourrisson **17**:1 (Jan.) 1929.

Between 800 and 1,000 infants less than 1 year of age and mostly less than 3 months are admitted annually to the nurseries of L'hospice des Enfants-assistés, an institution more than a century old. None of those admitted is in good health. There are many cases of hypothrepsia, syphilis and rickets, and many patients with various nutritional disorders; there are also infants with various diseases of the respiratory tract, skin and nervous system. For these patients, Marfan has tried to evolve a satisfactory type of feeding. He admits that breast milk is by far the most satisfactory food, but the difficulties of procuring it are sometimes insurmountable. Moreover, in former times wet nurses not infrequently contracted syphilis from infected infants. From 1921 to 1924, various artificial foods were tried out; ass's milk, goat's milk and various modifications of cow's milk. It was decided that cow's milk was faulty in two particulars: (1) The butter fat was too rich in volatile fatty acids, and (2) the quantity and quality of the casein rendered its digestion difficult. It was found that buttermilk would overcome these objections.

However, the mortality of infants on a diet of buttermilk was greater than that of infants on breast milk. It was decided, therefore, to employ wet nurses from whom the breast milk was expressed manually. This avoids the chance of syphilitic contagion, and the breast milk thus obtained is parceled out where it is most needed. Infants weighing less than 2,000 Gm. receive breast milk exclusively; this is also the diet of infants convalescing from a severe diarrhea. All others receive the mixed diet of breast milk and buttermilk; the breast milk should represent at least one third of the total ration. When the infants reach the age of 6 weeks or 2 months the buttermilk is replaced with a dilution of sweetened evaporated milk or a formula made from milk powder. As soon as the condition of the infant permits, the breast milk is discontinued and the ration is changed to regular cow's milk supplemented, at the age of 6 months, with farina broth. No infant is transferred to the country until it has demonstrated its ability to digest undiluted cow's milk. Under this regimen, the statistics show a decided improvement in the mortality rates, which thave been reduced from 50 per cent in 1920, to 30 per cent in 1923, 20 per cent in 1924 and 14.8 per cent in 1927. There has been a marked diminution in deaths from debility, athrepsia and diarrhea. The principal cause of death now is bronchopneumonia, especially when it is associated with an occult type of diphtheria.

PSYCHOSES OF LACTATION. M. MÉNACHÉ, Nourrisson **17**:43 (Jan.) 1929.

Two cases are reviewed in which mothers developed acute psychoses each time they nursed an infant. Weaning caused a fairly prompt return to normal behavior. The author believes that a mother developing an acute psychosis when nursing her first infant should not be urged or allowed to nurse subsequent children.

McCLELLAND, Cleveland.

IRRADIATED ERGOSTERIN AND THE ANTIRACHITIC VITAMIN D. G. TANRET, Paris méd. **4**:85 (Jan. 26) 1929.

Tanret reviews the literature to date and concludes that irradiated ergosterin is one of the most valuable agents in the treatment for rickets. When irradiated ergosterin is used, 5 mg. is equivalent to 1 liter of cod liver oil. Ergosterin should not be expected to replace heliotherapy, and should not be used without medical direction.

SANFORD, Chicago.

ARTIFICIAL INDIRECT HELIOTHERAPY IN RICKETS. EMILE WIELAND, Rev. franç. de pédiat. **4**:735, 1928.

A satisfactory irradiated dried milk was the subject of study. It contains 6 per cent sucrose and has been found to have a sufficient quantity of vitamin C to prevent the development of scurvy. By the use of from 50 to 80 Gm. of the

dried milk powder a day, patients with rickets were cured in the same manner and in the same time (from four to eight weeks) as with direct irradiation with ultraviolet rays. It was found, however, that if there was an infection of the upper respiratory tract or an infectious diarrhea, the healing was interrupted or delayed. In some cases irradiated ergosterol was found to be better tolerated than the irradiated milk. The dose should not exceed from 2 to 4 mg. a day. With this amount, there is no danger of the development of toxic symptoms or of the abnormal deposition of calcium salts.

Indirect artificial heliotherapy is specific for rickets and associated conditions such as tetany and osteomalacia. Its effect on other diseases and on healthy organisms (man and animal) should be studied further.

LESLIE, Evanston.

AN EXPERIMENT IN SUPPLEMENTING THE DIET OF SCHOOL CHILDREN. G. C. PAYNE and E. M. RIVERA, Porto Rico Rev. Pub. Health & Trop. Med. **4**:247 (Dec.) 1928.

School children were divided into four groups, each group contained twenty-four children. One group received milk as a supplement to the diet, one received bananas and two groups were used as controls. An unknown condition developed and all the groups lost weight. The group receiving milk, however, showed the least loss, and the group receiving bananas showed as great a net loss as the control groups. The results suggest that the addition of a small amount of milk to the diet may exercise a protective influence against adverse conditions. The addition of bananas did not appear to give a similar protection.

CONTROL OF THE MILK SUPPLY IN RIO DE JANEIRO. A. RODRIQUES, Arch. de pediat. Brazil **1**:68 (Dec.) 1928.

By a rigid control of the milk supply, the mortality from gastro-enteritis has dropped from 98 per 1,000,000 liters of milk consumed in 1920 to 57 per 1,000,000 liters of milk consumed in 1927.

ALIMENTARY INTOXICATION IN INFANTS. L. GONZAGA, Arch. de pediat. Brazil **2**:97 (Jan.) 1929.

In a discussion of the clinical forms and pathogenesis of intoxication, Gonzaga calls attention to the meningeal form, characterized by opisthotonos, and positive Kernig and Trousseau signs. A typhoid form resembles paratyphoid, and an asthmatic form shows pronounced dyspnea and respiratory disturbance. The author reviews the various theories of the causes of intoxication and comes to the conclusion that it is the result of a metabolic disturbance that is aggravated by a variety of factors.

ENERGY QUOTIENTS OF BREAST-FED CHILDREN IN THE HOSPITAL. U. NEUMANN, Arch. f. Kinderh. **85**:194 (Nov. 27) 1928.

From a comparison of the energy quotient values obtained by various authors and from his own experience, Neumann believes that Heubner's standard of 100 calories per kilogram of body weight as a minimum food requirement for breast-fed infants is subject to wide variations. The conditions under which the child lives and the factors existing in the mother or wet nurse may put the energy quotient lower than this standard. The child may, however, gain satisfactorily on this lowered amount.

EFFECT OF THE ULTRAVIOLET LIGHT ON THE BODY AND GROWTH OF THE CHILD. M. HAASE-KOEPPE, Arch. f. Kinderh. **85**:257 (Nov. 27) 1928.

This is the tenth article of this series, and deals with the rôle of phosphorus in phosphorized cod liver oil. The author found that after two months, fresh

neutral cod liver oil became both biologically and chemically acid. The same oil containing 0.01 per cent phosphorus remained biologically and chemically neutral after two months. Short exposures to ultraviolet light turned plain cod liver oil acid much sooner than normal and also affected the phosphorized oil. The optimum amount of phosphorus is 0.01, and higher concentrations appear to hasten the acid reaction. Neither the type of ultraviolet light nor the temperature had much effect on the reactions. Sesame oil and paraffin oil, either phosphorized or plain, were not turned acid by long exposure to ultraviolet light.

SANFORD, Chicago.

NUTRITIONAL EXPERIMENTS WITH WHOLE MILK. G. BESSAU, Monatschr. f. Kinderh. **42**:28, 1929.

In a short clinical experiment, Bessau tried feeding a number of children with whole milk plus rice gruel. Rice gruel was used on account of its relatively low fermentability. The children did rather well. The mortality of the children fed on dried milk was 3.2 per cent (three deaths among ninety-three children), due to the development of scurvy. Apparently, dried milk is deficient in vitamin C. Children weighing less than 2,500 Gm. did not do well on either of these mixtures; three out of five died. This may have been due, however, to an intestinal infection, although no organism was isolated.

SCURVY IN GUINEA-PIGS FED ON BREAST MILK. A. FRANK, Monatschr. f. Kinderh. **42**:177, 1929.

It is known that one can induce scurvy in guinea-pigs by feeding them oats and water. The rapid development of the disease on this diet destroys the animal's appetite, which, in turn, may be a factor in increasing the symptoms. To avoid this factor of undernutrition, the author substituted milk for water. Both cow's milk and human breast milk seem low in vitamin C. It is interesting to note that in a series of cases the guinea-pigs developed scurvy when fed on human breast milk. The addition of plasmon to the diet to overcome the factor of malnutrition did not change the course of the disease.

MILD NUTRITIONAL DISTURBANCES IN INFANTS WITH POSSIBLE SERIOUS CONSEQUENCES. WALTHER FREUND, Monatschr. f. Kinderh. **42**:192, 1929.

The author quotes Finkelstein as to the normal quantities of breast milk secreted during the first few weeks. In some of Freund's cases, the amounts secreted on the fourth or fifth day considerably exceeded the normal. Following this, there was a sharp diminution in secretion. If the physician is not alert, disturbances of nutrition may develop at this time.

THE WATER BALANCE IN INFANTS WITH NUTRITIONAL DISTURBANCE. JACOB JAHR, Monatschr. f. Kinderh. **42**:287, 1929.

In infants with nutritional disturbance and diarrhea, the water in the stool averaged 67 per cent, and in the urine 15 per cent. Three weeks later, when the children were well, 13 per cent water was in the stool and 55 per cent in the urine. These experiments confirm the clinical observations and also prove that the loss of weight during nutritional disturbance is not due to a high water content of the stool. In the author's cases, the children did not lose weight. Loss of weight occurs only when the water is squeezed out of the cells.

DYSENTERY IN INFANTS TREATED WITH CREAM MIXTURE. ALBERT UFFENHEIMER and GEORG LAMPRECHT, Monatschr. f. Kinderh. **42**:445, 1929.

The writer added 10 per cent cream, with a caloric value of 129 per 100 cc. to the diets of infants with bacillary dysentery. He started with from 50 to 100 cc.

and increased the amount gradually so that by the end of the second year the dose was from 300 to 400 cc. In exceptional cases, older children were given as much as 750 cc. a day. The children took the mixture well, and recoveries occurred without marked loss of weight. The mixture seemed to have a beneficial effect on the stools, and coincidental with improvement of the stool came improvement in the general condition. Recurrences and complications were rare. Contraindications to the treatment are the age, in children less than 3 months old, severe nutritional disturbance and severe complications such as pneumonia. The treatment is to be stopped at any time when the bowel movements become sufficiently fluid to show duodenal contents.

GERSTLEY, Chicago.

Prenatal Conditions

CONGENITAL STENOSIS OF THE OESOPHAGUS. C. C. BEATTY, Brit. J. Child. Dis. **25**:237 (Oct.-Dec.) 1928.

This paper is based on a detailed study of fifty recorded cases and two others which came under the author's observation. Pathologically, there are two types of congenital narrowing of the lumen of the esophagus: (1) In one type a thin diaphragm of mucous membrane is stretched across the interior of the tube with a clearcut opening which varies in size in different cases, the external dimension of the esophagus being unchanged. The membrane is usually situated at either the upper or the lower end of the esophagus. (2) In the other, there is an actual narrowing of the whole tube for a variable longitudinal distance of variable degree. All the different coats at the site of the narrowing are normal.

Later changes that take place are: (1) hypertrophy of the muscular coats of the esophagus, both longitudinal and circular, and (2) dilatation of the esophagus above the obstruction.

The cause of this congenital anomaly is not known. The symptoms and signs usually appear in infancy, though in some instances the onset is in middle life. Often, attention is first called to the condition when the infant is given solid food for the first time. This results in regurgitation of the food, not in true vomiting. The degree of difficulty in swallowing varies considerably from time to time.

If the patient survives the first few years of life, there is a reasonable prospect that he will attain old age if the limitations as to diet are realized and acted on. The prognosis in the membranous type of the condition is more favorable. This type yields to treatment (gradual dilatation with bougies, controlled by esophagoscopy), whereas in the other type dilatation is unlikely to be successful and is attended by the risk of rupture.

LANGMANN, New York.

A CASE OF DOLICHOSTENOMELLA (ARACHNODACTYLIA). ZUBER and COTTENOT, Bull. Soc. de pédiat. de Paris **26**:311 (June) 1928.

The patient was a girl, aged 5 years, who since birth had had large hands and long feet; she sat up at the age of 2½ years, and walked at 3½. She was 95 cm. tall, 102 cm. being normal. She was thin (weight not given), and the four extremities were long and slender. The cranium was elongated with a median prominence, especially at the frontal suture. The ears were poorly formed; a slight strabismus was present; the uvula was bifid, and there was a spina bifida occulta. The child was backward and hardly spoke words. Roentgenologic examination confirmed the presence of long slender bones and the spina bifida occulta and showed premature ossification of the scaphoid and trapezoid carpal bones; the long bones, more especially the metatarsals and the fibulae, showed thickening of the cortex and narrowing of the medullary cavity, and the sella turcica was narrow because of the thickened anterior and posterior clinoid processes. The question of the hypophysis possibly being at fault in this condition is mentioned.

Two Cases of Bilateral Radial Deformity of the Hand Due to Congenital Absence of the Radius. M. Roederer, Bull. Soc. de pédiat. de Paris **26**:373 (July) 1928.

Although the condition occurs twice as often in boys, the author's cases were both in girls, aged about 2 months when first seen. Both showed flexion deformity of the hand on the forearm and of the forearm on the arm, and complete luxation of the hand. One infant had a thumb on each hand; the third toe of each foot showed a hammer deformity. The other infant had no thumbs and only rudimentary fingers, with no other deformity of the entire body.

Benjamin, Montreal.

Acrocephaly-Syndactylism with Facial Dysostosis. E. Lesné; R. Clément and Gilbert-Dreyfus, Bull. Soc. de pédiat. de Paris **26**:488 (Dec.) 1928.

A full account is given of the case of a girl, aged 14 years, with typical acrocephaly and syndactylism, combined with the facial deformities described by Crouzon. Apert's discussion adds to the article.

Congenital Malformations of the Lower Extremities. A. Trèves, Bull. Soc. de pédiat. de Paris **26**:496 (Dec.) 1928.

A child, aged 2 months, suspected of being syphilitic in spite of a normal family history, was born with scars over both knees and with clubfoot. The orthopedic treatment is outlined.

Two Cases of Congenital Lacunae of the Cranial Vault. B. Weill-Hallé and J. Weill, Bull. Soc. de pédiat. de Paris **26**:497 (Dec.) 1928.

Two children presented oval defects in the flat bones of the head: in one case, a single defect involving both the right parietal and the frontal bone; in the other, two defects each involving a parietal bone. There was no other skeletal anomaly. The authors felt that they could exclude syphilis, tuberculosis, mycosis, cleidocranial dysostosis, periosteal dysplasia, amniotic adhesions causing epicranial defects, hydrocephalus and craniotabes; they classified their cases with those of Crouzon as "congenital lacunae of unknown nature."

Congenital Hernia of the Lung with Complex Malformations of the Thoracic Wall. Lereboullet; A. Bohn and R. Worms, Bull. Soc. de pédiat. de Paris **26**:500 (Dec.) 1928.

The authors describe the case of a boy, aged 12½ years, with congenital absence of the pectoralis major muscle and of the mammary gland of the right side; and arrest in development of the third, fourth, fifth and sixth right ribs, which failed to reach the sternum. The lung herniated through the hiatus thus formed. The literature is given.

Clausen, Rochester, N. Y.

Diseases of the New-Born

Cephalematoma and Unilateral Maxillary Subluxation in a New-Born Infant. Georges Schreiber, Bull. Soc. de pédiat. de Paris **26**:319 (June) 1928.

The patient was a girl, aged 6 weeks, who had been delivered normally. A cracking sound at each sucking movement was noted the day after birth; this was due to subluxation of the right jaw. The mother and one of her sisters showed a congenital laxity of both elbow joints.

Benjamin, Montreal.

RESPIRATORY EXERCISES FOR THE NEW-BORN INFANT. P. DESFOSSES, Presse méd. **11**:184 (Feb. 6) 1929.

The author quotes Pierre Robin of the Infants' Hospital of Paris to the effect that the majority of nasal infections of later life are due to improper breathing in childhood. Primitive mothers nurse their infants in an upright position so that the child's nose is free. European mothers usually compel their children to nurse in a prone position, so that the nose is partially buried in the breast. As this may account for many nasal troubles, a more upright position is advocated. This should begin in the first days of life, so that the infant is trained to breathe its full lung capacity.

SANFORD, Chicago.

PATHOGENESIS OF ICTERUS NEONATORUM. W. G. SCHULTZ, Ztschr. f. Geburtsh. u. Gynäk. **94**:793 (Feb.) 1929.

Schultz investigated the pathogenesis of icterus neonatorum. In fetuses, aged from 4 to 6 months, he found no evidence of erythrophagocytosis or much deposition of iron in the reticulo-endothelial cells of the spleen or liver. In premature and new-born infants, the extent of the phagocytosis of red cells and the deposition of iron in the spleen and liver were directly proportional to the number of hours or days the infant lived. The long duration of the high bilirubin content of the blood after birth opposes the theory that retroplacental hemorrhages are the cause of the icterus. The author considers the usual icterus neonatorum a result of hyperactivity of the reticulo-endothelial system. The cause of this hyperactivity cannot be explained. No evidence of defective excretion of the liver was found.

BRAHDY, New York.

Acute Infections

THE MEDICAL SOCIETY'S SHARE IN PROTECTING THE CHILDREN OF SCHENECTADY AGAINST DIPHTHERIA. HOWARD A. GILMARTIN, New York State J. Med. **28**:1097 (Sept. 1) 1928.

The campaign in Schenectady was advised by the committee on Public Health and Medical Education of the State Society as a demonstration. The County Medical Society appointed a committee of eight members to represent the society during the campaign.

During the first year, all cases were referred to the family physicians who charged a uniform fee for three injections. Every effort was made to interest parents in the work. After one year, the second stage of the campaign began with the opening of a clinic for free immunization. A third stage is still to be carried out in an effort to reach the preschool children who have not been immunized. "Our community is educated to the fact that the family physician can administer this treatment at a cost within reach of 95 per cent of the population."

The pamphlets distributed avoided the use of the term toxin-antitoxin, anticipating the possibility of other preparations such as toxoid or anatoxin being used in the future.

As a result of this campaign Schenectady, with a population of 95,000, had only one death from diphtheria in twenty months.

AIKMAN, Rochester, N. Y.

CURRENT WORLD PREVALENCE OF COMMUNICABLE DISEASES. Pub. Health Rep. **44**:476 (March 1) 1929.

In a survey of the United States from Jan. 6 to Feb. 2, 1929, meningococcus meningitis showed the highest attack rate for that disease since 1918. The rate for influenza had approached normal, and that for measles gave only a slight increase. Scarlet fever, diphtheria, poliomyelitis and typhoid fever showed a low level, or a decrease.

SANFORD, Chicago.

THE EPIDEMIOLOGY OF UNDULANT FEVER. C. N. KAVANAUGH, South. M. J. **22**:290, 1929.

The author finds that the *Brucella melitensis* variety of abortus infection is widely prevalent in cattle throughout the country.

The close relationship between *Brucella melitensis* of goats and *Brucella abortus* occurring in cattle and hogs is definitely established.

The organism is pathologic to man and produces a disease with a distinct clinical entity. The condition is endemic in the southwestern part of the United States.

Children under 8 years of age apparently have a high degree of immunity. Direct contact with infected animals and the common utilization of raw milk is the essential cause of undulant fever in the United States.

Universal pasteurization of milk is essential for the control of undulant fever.

SCHLUTZ, Minneapolis.

THE RHEUMATIC CHILD. N. GRAY HILL, Brit. J. Child. Dis. **25**:270 (Oct.-Dec.) 1929.

The author examined 400 children, the majority of whom showed evidence of acute rheumatism or one of its manifestations. In all of them the diagnosis of some form of rheumatism had been made before admission. Records were taken of the color of the hair and eyes, the texture of the skin, the condition of the teeth, the diet, the condition of the tonsils and the mental make-up. This investigation was made because of the impression that rheumatism was more frequently found in children with red or fair hair, with decayed teeth and with a particular mental make-up (emotional, bright and vivacious). As a result of this study, "no physical characteristics were found that were peculiar to rheumatic children other than those that were the outcome of the disease."

EROSION OF THE NECK VESSELS IN SCARLET FEVER: A RECORD OF TWO CASES. J. D. ROLLESTON and W. GORDON SEARS, Brit. J. Child. Dis. **25**:281 (Oct.-Dec.) 1928.

In the course of an attack of scarlet fever an infant boy developed swollen glands on the right side of the neck, then profuse right-sided otorrhea and, a few days later, severe hemorrhage from the right external auditory meatus with an increase in the size of the swelling on the neck. An incision of the latter revealed serum and a blood clot. At autopsy, an abscess cavity lying deep and to the right of the sternomastoid muscle was found. The external carotid artery and its branches and corresponding veins were surrounded by inflammatory tissue. It seemed probable that one of the veins had been eroded, though no definite point of erosion was found. The second child, a girl, aged 2 years and 4 months, had septic scarlet fever complicated by erosion of the tonsils, palate and tongue, bilateral suppurative adenitis and bronchopneumonia. The glands on both sides were incised. There was a profuse hemorrhage from the left side. Autopsy showed erosion of the left jugular vein. According to the authors, erosion of the vessels of the neck giving rise to fatal hemorrhage is a rare event and occurs in practically only two conditions, namely, scarlet fever and gangrenous angina.

TREATMENT AND PROPHYLAXIS OF SCARLET FEVER WITH SPECIFIC ANTITOXIC SERUM. JAMES C. B. CRAIG, Lancet **2**:1123 (Dec. 1) 1928.

Five hundred patients with scarlet fever were treated at the Edinburgh City Fever Hospital. The results were distinctly favorable. The author recommends that at least 5 cc. be used as a prophylactic dose. In the treatment for the disease he found that if the serum is given within the first three days it produces a favorable effect in counteracting the toxemia, and the reactions are not severe. It also lessens the incidence and severity of subsequent complications. In order to get the best results, the full therapeutic dose should be given at the earliest possible moment.

LANGMANN, New York.

PSEUDODIPHTHERIA IN THE INFANT. CASSOUTE and MONTUS, Bull. Soc. de pédiat. de Paris **26**:361 (July) 1928.

Because of the repeated reports of numerous cases in which cultures from the nose and throat showed the presence of *B. diphtheriae* in infants in the nurseries of Paris, the authors studied 170 cases in an institution and found no Klebs-Loeffler bacilli, but diphtheroid bacilli in 54. Suggestive bacilli grown on blood serum slants were transferred to broth and blood agar so that their hemolytic properties might be studied, and when it was deemed necessary, injections of some were made into guinea-pigs. The authors conclude that true diphtheria is rare in infants, contrary to many recent reports, and that the bacillus should be definitely isolated before antitoxic serum is given.

ATTEMPT TO PREVENT SCARLET FEVER BY THE USE OF ANTISCARLATINAL SERUM. RENE MARTIN and ALBERT LAFFAILLE, Bull. Soc. de pédiat. de Paris **26**:364 (July) 1928.

At the onset of epidemics of scarlet fever in two children's institutions, the authors picked out the susceptible children by positive reactions to Dick tests and by the injection of antiscarlatinal serum (20 cc. for those over 14 years of age and 10 cc. for those under that age). All but one of these children were rendered negative to the Dick test. The susceptible children who were rendered negative remained so for about three weeks, after which time the reactions became positive again and several children developed scarlet fever.

ANTISCARLATINAL SEROTHERAPY; RESULTS OBTAINED IN TWENTY-TWO SEVERE CASES. NOBECOURT, Bull. Soc. de pédiat. de Paris **26**:369 (July) 1928.

The serum should be reserved for only severe forms of the disease. When given, it produces marked improvement in the initial toxemia, but does not prevent suppurative complications or secondary infections.

BENJAMIN, Montreal.

GONORRHEAL ARTHRITIS IN A CHILD 3 YEARS OLD. MARIA TERESA VALLINO and JOSÉ MARIA MACERA, Arch. latino-am. de pediat. **22**:779, 1928.

The authors report a case of gonorrheal arthritis in a child, aged 3 years. The arthritis was confined to the lower extremities and involved particularly the joints of the feet. A severe gonorrheal vulvovaginitis had existed for two weeks previous to the manifestations of involvement of the joints. The condition yielded fairly promptly to the treatment with antigonococcic vaccine and local treatment of the vulvovaginal condition.

SCHLUTZ, Minneapolis.

Chronic Infections

EARLY DIAGNOSIS AND EARLY RADICAL OPERATION IN TUBERCULOUS LYMPH GLANDS OF THE NECK. JOHN HANFORD, New York State J. Med. **29**:1159 (Oct. 1) 1928.

For the past twenty years, surgery has been giving way to more conservative forms of treatment for tuberculous adenitis. While heliotherapy, removal of foci of infection, diet, rest, fresh air and other therapeutic measures are of value, surgery is now becoming recognized as the best method of treatment. Diagnosis must be made early and the patients given skilful surgical treatment. At the same time rest, fresh air and other measures commonly used may be carried on. More than 400 cases of tuberculous adenitis have been studied in the special clinic of the Presbyterian Hospital (New York City); in about 74 per cent the condition was beyond the early favorable stage. In the study presented of 69 children, aged 15 years and under, 62.4 per cent were found beyond the favorable stage. Only five were in an ideal stage for clean successful operation.

Early diagnosis is made possible by considering glands from 1.5 to 2 cm. in diameter suggestive if they have persisted from six to eight weeks without evidence of much acute inflammation. Sterile cultures of "pus," examinations of sections of removed tonsils, roentgen examination and biopsy, especially, are of great value. Biopsy should usually consist of a complete radical excision. Tuberculin skin tests cannot be relied on in these cases.

This study confirms the evidence that radical excision in patients with localized tuberculous cervical adenitis gives apparently permanent cures in 90 per cent so treated. The earlier the diagnosis, the better is the result. Iodine and other local irritants induce and hasten the spread of the disease.

The operation should be done as soon after the diagnosis is made as possible, in order to avoid possible extensive liquefaction which may occur in two or three days and which will interfere with the good results.

AIKMAN, Rochester, N. Y.

DRAINAGE OF COLD ABSCESSES IN THE RESPIRATORY AND DIGESTIVE TRACTS. M. LANCE, Bull. Soc. de pédiat. de Paris **26**:298 (June) 1928.

It is important to determine whether or not the abscess communicates with the pleural cavity. When there is no intrapleural opening, the condition is compatible with long life, even when fistulas of the skin are present; when an intrapleural opening exists, the prognosis is grave. If there is an opening into the esophagus, the prognosis is also bad. Regarding retropharyngeal cold abscess, the author quotes a statement that in more than half of those opened by the pharyngeal route recovery is obtained; he takes issue with this statement and advises drainage by the cervical route.

RESULTS IN TWENTY INFANTS IMMUNIZED WITH B. C. G. HENRI LEMAIRE and LOUIS WILLEMIN-CLOG, Bull. Soc. de pédiat. de Paris **26**:327 (June) 1928.

The authors' experience with the Pirquet reaction is stated thus: With a negative or faintly positive Pirquet reaction there are no clinical or roentgenologic signs of tuberculosis (a faintly positive reaction is due to attenuated bacilli). With clinical or roentgenologic evidence of localized tuberculosis — pulmonary or hilum tuberculosis tracheobronchial lymphadenitis, or tuberculosis of the skin or bone — there has been spontaneous infection with virulent bacilli, and the source of contamination can usually be found.

The authors divide the cases according to whether the Pirquet reaction is negative, faintly positive or strongly positive. The twenty cases showed the following reactions: (1) two cases, entirely negative, in spite of direct contact; (2) two cases, entirely unfavorable results, despite correct conditions of vaccination; (3) five cases, positive infection (these patients were not separated from the infected person for any time) and (4) eleven cases, negative (these patients were never exposed).

The authors conclude that B. C. G. is immediately innocuous, and that it gives only relative, not absolute, immunity. The five weeks' isolation, recommended by the authors, of patients inoculated with B. C. G. is not indispensable for relative immunity.

THE VALUE OF IMMUNIZATION WITH B. C. G. IN TUBERCULOUS ENVIRONMENTS (IMMUNIZATION OF INFANTS). WEILL-HALLE, TURPIN, BENDA and COLONI, Bull. Soc. de pédiat. de Paris **26**:345 (July) 1928.

This study includes 137 infants in tuberculous environments, regularly examined and visited by nurses, observed mostly for more than one year.

The results were divided as follows: group A, born of tuberculous mothers: forty-three infants, of whom nine died; in one, tubercle bacilli were found, three died in the first ten days of life during an epidemic in the nursery, three died of bronchopneumonia, and in two the cause of death was undetermined; group B, born of healthy mothers, but having tuberculous contact: sixty-four found to have tuberculosis, and of these six died, one of tuberculosis of the spine and knee, two

of gastro-enteritis, one after convulsions, and one of bronchopneumonia with measles; thirty showed no evidence of tuberculosis, and of these one died of bronchopneumonia.

The gross mortality rate was 11.5 per cent, and the mortality rate from tuberculosis, 3 per cent. The authors emphasize prophylaxis, which means separation, especially during the period of immunization. The deaths from tuberculosis occurred in those who had not been isolated and who had been in contact with the infection from the beginning of life. To obtain the best results with B. C. G., there should be separation from contact for at least one month—if necessary, the expense of this should be paid by charity. The authors are following a group of non-immunized persons in contact with tuberculosis. They conclude that B. C. G. has incontestable value for immunization.

THE TUBERCULIN REACTION AND ANTITUBERCULOSIS VACCINATION. ROBERT CLEMENT, Bull. Soc. de pédiat. de Paris **26**:357 (July) 1928.

The author quotes a printed note which accompanies each ampule of B. C. G. from the Pasteur Institute, which says that the tuberculin reaction has no significance in vaccinated children and advises against its use. Clement has never seen any harm from the tuberculin skin test and believes that it is of value in following these children. He therefore makes a plea that the Société express a desire that this note be removed from the packages of B. C. G. vaccine.

BENJAMIN, Montreal.

THERAPEUTIC RESULTS OBTAINED WITH A MEDICAMENTAL SERUM IN PULMONARY GLANDULAR TUBERCULOSIS OF EARLY LIFE. M. DUFOUR, Bull. Soc. de pédiat. de Paris **26**:480 (Dec.) 1928.

The serum consists of one part of the serum of a rabbit which had been given a quantity of crude tuberculin, and of two parts of an aqueous solution of hexamethylene tetramine-methyliodide (Hurez, Paris Thesis 1927). An injection of 3 cc. was given twice a week for about ten weeks to four children, aged 13 months, 1 year, 7 months, and 6 months, respectively, who had tuberculosis of the tracheobronchial glands as proved by roentgen examination and positive results from skin tests. Great improvement followed in each patient. One child developed spina ventosa, and another tuberculosis of the hip, but all patients eventually made excellent progress within a year. No mention is made of any other therapeutic measures. Failures are not reported. Reference is made to the successful use of this serum in adults. It is useless in tuberculosis meningitis and in advanced pulmonary tuberculosis with excavation.

SEVERE SYPHILITIC ICTERUS. L. RIBADEAU-DUMAS, CHABRUN AND ROUQUES, Bull. Soc. de pédiat. de Paris **26**:504 (Dec.) 1928.

Two patients showed typical diffuse syphilitic hepatitis at autopsy; in neither case could spirochetes be demonstrated.

COEXISTENCE OF PURE MITRAL STENOSIS, LUPUS, AND SPINA VENTOSA IN A CHILD ELEVEN YEARS OLD. B. WEILL-HALLÉ and J. WEILL, Bull. Soc. de pédiat. de Paris **26**:515 (Dec.) 1928.

In this case, no cause for the mitral stenosis seemed probable except tuberculosis. The literature on the subject is cited.

CLAUSEN, Rochester, N. Y.

A CASE OF TUBERCULOSIS IN A NEW-BORN INFANT. A. BARVOZA, Arch. de pediat. Brazil **1**:16 (Oct.) 1928.

The infant developed a temperature of 38 C. (100.4 F.) on the twenty-seventh day of life. The spleen was palpable and some cervical adenitis was present. Facial paralysis developed on the thirty-seventh day, followed by convulsions. A mas-

toidectomy was done, and considerable caseous pus was found. The infant died two days after the operation and autopsy showed extensive generalized tuberculosis. The Mantoux reaction remained negative throughout the illness.

SANFORD, Chicago.

ACUTE TUBERCULOUS CERVICAL ADENOPATHY. HANS FERNBACH, Monatschr. f. Kinderh. **42**:170, 1929.

The author reports seven cases in which the symptoms developed in periods varying from a few days to two weeks. He does not know how to explain this fact. It shows, however, that one should make careful diagnoses so as not to overlook such cases.

TRANSFERRING SPIROCHAETA PALLIDA FROM THE LYMPHNODE OF AN INFANT WITH LATENT SYPHILIS TO A RABBIT. RICHARD HAMBURGER, Monatschr. f. Kinderh. **42**:198, 1929.

In an infant with latent syphilis, a cubital and an inguinal lymph gland were removed; each was inoculated into the testicle of a rabbit. Inoculation of other rabbits with the blood of the child gave no results. The rabbits inoculated with the lymph nodes developed syphilis. The Wassermann reaction of the infant was positive.

GERSTLEY, Chicago.

Internal Diseases

UROLOGIC CONDITIONS ENCOUNTERED IN CHILDREN. B. A. THOMAS and J. C. BIRDSALL, J. A. M. A. **91**:1428 (Nov. 10) 1928.

With a few exceptions children present the same urologic lesions that adults do and should be given the same thorough examinations. Pyuria and hematuria indicate early and complete urologic study. Early diagnosis and appropriate surgical treatment will usually prevent extensive and permanent renal injury. No child, apparently, is too young to undergo a complete urologic investigation owing to the perfection of the modern cystoscope designed for children and infants.

URINARY CALCULI IN CHILDREN. CLINTON K. SMITH, J. A. M. A. **91**:1431 (Nov. 10) 1928.

Five cases of urinary calculi in children are reported. The etiology of urinary calculi in children does not present any more special features of interest than it does in adult life, but the author is of the opinion that one must look for the beginning of calculi in childhood although the stones may not be found until adult life. There is no essential difference between the urologic problems of childhood and those of adult life. The methods of cystoscopic precision in diagnosis and treatment are equally practical in both age groups. Calculi occur in practically the same ratio as in adults. Routine roentgenograms should be made in all cases in which a diagnosis of pyelitis is made or when hematuria or persistent pain occurs. The apparent tendency to recurrence warrants the elimination of all focal infections, the maintenance of good urinary drainage and frequent reexaminations.

BONAR, Salt Lake City.

1. INTENSE ASCITES? HEPATIC SYPHILIS. 2. TUMOR OF FACE. ASTLEY V. CLARKE, Proc. Roy Soc. Med. **21**:95 (Oct.) 1928.

(1) a boy, aged 13 years, was admitted to the hospital with a severe case of ascites. He gave a history of illness for the previous eight weeks, but the swelling in the stomach had been present for only one week. The father and mother were well. There were five other children. Paracentesis was performed three times in less than three weeks; each time, from 12 to 15 pints (6.8 to 8.5

liters) of fluid was withdrawn. Nothing abnormal could be felt in the abdomen after withdrawal of the fluid. The treatment consisted of ultraviolet light and mercury, with increasing doses of potassium iodide. No evidence of tuberculosis could be obtained, but investigation of the case showed that the kidneys were involved early in the history.

(2) In a boy, aged 13 years, the growth began eighteen months before admission, and grew rapidly at first; then it appeared to stop, but again its growth became rapid about December, 1917. The report is accompanied by pictures of the patient and x-ray pictures of the bones of the face.

(1) Congenital Malformation of Pelvis and Lower Extremities. (2) Raynaud's Disease. (3) Osteogenesis Imperfecta. (4) Fibrocystic Disease of Left Humerus Showing Spontaneous Cure. Robert S. Lawson, Proc. Roy. Soc. Med. **21**:1850 (Oct.) 1928.

(1) A child, aged 3 years, showed marked deformity of the hips, both legs being widely abducted. The child lay in the frog position and had an extra thumb on the right hand. The report is accompanied by an x-ray picture.

(2) A case of Raynaud's disease was reported in a patient, aged 2½ years.

(3) A girl, aged 12 years, had pain in the back which was found to be rigid in the lumbar region. Blueness of the sclerotics suggested osteogenesis imperfecta. On inquiry it was found that the patient had had fractures of several bones and that her father had had seven fractures before he was 6 years of age.

In light of these facts it was thought probable that this patient had sustained a fracture of one of the vertebrae which had caused a temporary rigidity of the spinal muscles. This fracture did not appear in the x-ray plates, but defective ossification of the bones of the vertebrae were shown, a defect common to all other bones.

(4) A boy, aged 14 years, gave a history of fracturing his arm one year before he reported a fracture of the same arm. A roentgenogram showed no fracture, but revealed a condition resembling either a myeloma or fibrocystic disease in the metaphysis of the left humerus. As the boy had no symptoms it was considered unnecessary to operate, but he was kept under observation. Roentgenograms taken from time to time showed the bone returning to normal. The spontaneous cure supports the opinion that the condition is either traumatic in origin or caused by a defect in metabolism during the period of growth.

(1) Hypertelorism. (2) Myositis Ossificans Progressiva. (3) Infantilism and Hypertrichosis. (4) Osteogenesis Imperfecta. J. V. C. Braithwaite, Proc. Roy. Soc. Med. **21**:1857 (Oct.) 1928.

(1) Hypertelorism was reported in a girl, aged 2 years. Backwardness was noticed at the age of 15 months. The eyes were widely separated and the face was flat with a receding chin.

Measurements of the eyes and head as well as photographs of the patient are given in the report. The patient was put on solution of pituitary and showed a marked improvement.

(2) A case of myositis ossificans was reported in girl, aged 7 years. The report is accompanied by photographs of sections of muscles, a picture of the patient, and x-ray plates showing muscles at the various stages of the disease. The blood count is also given. The Wassermann reaction was negative.

(3) and (4) A case of infantilism and hypertrichosis was reported in a patient, aged 13 years, and a case of osteogenesis imperfecta in a patient, aged 3 years.

Muscular Hypotonia with Hypoglycemia. C. Worster-Drought, Proc. Roy. Soc. Med. **22**:133 (Dec.) 1928.

The author reported the case of a boy, aged 8 years, who was brought to the hospital because he was unable to balance himself properly and was backward at

school. On examination, he was found dull mentally. His speech was indistinct, and he walked slowly and with difficulty. Muscle tone was much decreased. Coordination and sensations were normal. There was a low "leak-point" for sugar. The family and past history as well as a description of the previous health of the patient are given in the report. WILLIAMSON, New Orleans.

A CASE OF LEFT SUBDIAPHRAGMATIC ABSCESS. NOBECOURT, BOULANGÉR-PILET, KAPLAN and ARMINGEAT, Bull. Soc. de pédiat. de Paris **26**:320 (June) 1928.

A boy, aged 14 years, whose illness began with loss of appetite and weight, was put to bed for about three months, with the diagnosis of chronic splenomegaly. He did not improve and was sent to the hospital. About two months previously he began to cough and produced sputum which soon became purulent and fetid. The injection of iodized oil 40 per cent after surgical drainage two fingerbreadths above the left twelfth rib and then a roentgenologic examination showed the abscess to be located in the perisplenic space, with left pyopneumothorax which had opened into a bronchus. The spleen was pushed downward and forward. The child's general condition improved, and he began to put on weight after the surgical intervention.

ROENTGENOLOGIC EXAMINATION OF INFANTS WITH PERICARDITIS. P. DUHEM, Bull. Soc. de pédiat. de Paris **26**:339 (June) 1928.

The three roentgenologic features are: the marked enlargement of the cardiac shadow, due to the effusion which distends the pericardium and extends the left border of the cardiac shadow to the axilla; the clear outline of this shadow, due to the absence of beats, and the relative narrowness of the basal vascular shadow compared with the body of the heart, because the pericardium does not encircle these great vessels.

Pericardial adhesions, total or partial, can usually be made out. When the entire contour of the pericardium shows irregular projections, there are generalized pleuropericardial adhesions. Partial adherence to the diaphragmatic pleura is indicated by the heart moving with the movements of the diaphragm; this does not occur normally, and the diaphragmatic movements are somewhat restricted. When the adhesions are fastened to the mediastinal pleura the heart does not follow the diaphragmatic movements. A left basal pleural effusion may mask the left cardiac border and conceal the beats, rendering the diagnosis difficult. In conclusion, the author adds that it is impossible for roentgenography always to determine whether enlargement of the cardiac shadow is myocardial or pericardial.

BENJAMIN, Montreal.

SPLENOMYELOID ANEMIA, AND FAMILIAL ANEMIA: THE EFFICACY OF HEROIC TREATMENT. J. CATHOLA and MLLE. BOEGNER, Bull. Soc. de pédiat. de Paris **26**:484 (Dec.) 1928.

The mother of the patient, aged about 30 and of pale complexion, had had one miscarriage, one infant which died of anemia at the age of 5 months, one anemic daughter, aged 6 years, and another child who is reported here. This child, aged 16 months, had never eaten solid food or vegetables in any form, and was obviously rachitic. The liver and spleen were extremely large, and the blood picture was that of pseudoleukemic anemia. The Wassermann reaction was negative. The child developed repugnance to liver soon after a liver diet was begun. The "heroic" treatment was then begun, consisting of ferrous oxalate, 0.1 Gm. per day, administered for two months. (The method of administration was not mentioned.) Rapid improvement followed.

Tixier, in a discussion, recommends antisyphilitic treatment, even when the Wassermann reaction is negative, in case the administration of iron is ineffective.

PAROXYSMAL TACHYCARDIA AND POLYPNEA IN AN INFANT. J. HUBER and M. ENACHESCO, Bull. Soc. de pédiat. de Paris **26**:544 (Dec.) 1928.

A male infant was observed, between the ages of 3 and 7 months, in several attacks of tachycardia (in which the pulse rate was as high as 200 per minute) and of polypnea (in which the respiratory rate was as high as 80 or more per minute). Each attack lasted for several days and was accompanied by fever of undetermined origin. The authors found a shadow in the mediastinum on the right side, probably not thymic.

CLAUSEN, Rochester, N. Y.

SOME ASPECTS OF DIABETES IN THE YOUNG. WAGNER, Rev. Internat. de l'enf. **7**:15, 1929.

In a study of the English mortality rate, Pirquet came to the conclusion that diabetes in the young has not contributed to the increased death rate from this disease since 1838. The great majority of deaths from diabetes mellitus occur after the age of 45. In children there appear to be two periods of special susceptibility, the first between the ages of 2 and 4 and the second between 8 and 10. As observed by all clinicians, the evolution of the disease is much more rapid in the young than among adults; its course is aggravated frequently by the appearance of intercurrent diseases which are so difficult to prevent in early life. Regarding the much discussed question of heredity, Wagner believes that it has a distinct bearing on the disease, though he is unable to furnish any satisfactory proof. He finds among his sixty-five cases that stigmas are common as are also errors of development. One of the most serious and, unhappily, most frequent complications of diabetes is tuberculosis. Here the blood sugar curve is somewhat different, and much larger doses of insulin are required. Wagner submits four important types of diet: the adjustment type, the maintenance diet, a superalimentation diet for children much underweight and a special carbohydrate regimen in those cases in which the tolerance is lowered through intercurrent infections.

AMESSE, Denver.

HYDATID CYST OF THE LEFT LUNG WITH DISPLACEMENT OF THE HEART AND NONTUBERCULOUS SEROFIBRINOUS PLEURISY. JOSÉ BONABA, ROGELIO CHARLONE and VICTOR ESCARDÓ ANAYA, Arch. latino-am. de pediat. **22**:764, 1928.

The authors report a case of hydatid cyst in the left lung of a boy, aged 12 years. The location of the cyst was masked by an extensive pleurisy with effusion over the left lung.

There was marked displacement of the heart. Tuberculin tests and examination of the chest for bacilli were negative. The pleurisy and effusion were apparently due to the proximity and the influence of the hydatid cyst. Repeated drainage of the cyst was accompanied by excessive vomiting and anaphylactic phenomena.

SCHLUTZ, Minneapolis.

A CASE OF MITRAL STENOSIS. M. DE ROCHA, JR., Arch. de pediat. Brazil **1**:14 (Oct.) 1928.

A boy, aged 10 years, presented a typical mitral stenosis, with an enormously enlarged heart. The Wassermann reaction was positive. While under treatment, he developed influenza which resulted in decompensation. Cirrhosis of the liver complicated the case, but the boy recovered. Roentgenograms taken afterward showed the heart much more enlarged than before.

A CASE OF INTERLOBAR EMPYEMA. M. DE ROCHA, JR., Arch. de pediat. Brazil **1**: 77 (Dec.) 1928.

A boy, aged 9 years, developed a fever and difficult respiration four days after a football accident. Examination showed a fractured rib and a peculiar

condition in the lung which the roentgenogram showed to be an interlobar empyema. The author believes that this happens more frequently than is usually supposed.

THE USE OF PHENYL SALICYLATE IN PYURIAS. M. OLINTO, Arch. de pediat. Brazil **1**:80 (Dec.) 1928.

In several cases, the author successfully used phenyl salicylate in doses of from 0.05 to 0.2 Gm. (¾ to 3 grains) given from five to eight times a day.

A CASE OF PARATYPHOID PYELITIS. E IMBASSAHY, Arch. de pediat. Brazil **2**: 122 (Jan.) 1929.

A girl, aged 14 months, with pyelitis was given the usual treatment with no clinical improvement. Culture showed paratyphoid *Salmonella*. Recovery was rapid after the administration of an autogenous vaccine. The author expresses his belief that many cases of pyelitis considered as caused by *Bacillus coli* are, in fact, caused by the paratyphoid bacillus. These conditions will not improve under the ordinary therapy, but are amenable to autogenous vaccine.

PNEUMONIA SYNDROME IN THE INFANT. C. PELFORT, Soc. Argentine de pediat., Dec. 6, 1928.

In the majority of infants with pneumonia the condition is frank lobar pneumonia, but bronchopneumonia and pseudolobar pneumonia are often difficult to distinguish. For this reason, the author prefers to call them the "pneumonia syndrome." The upper lobe of the right lung and the lower lobe of the left lung are most often affected. The condition is most prevalent during the winter; spring is next in point of frequency, and then autumn and summer. Crises terminated 70 per cent of the cases, and lysis, 20 per cent. The crisis occurred on the seventh day in 40 per cent of the cases, between the third and sixth days in 28 per cent, and after the seventh day in 32 per cent. The most frequent complication was otitis media, which occurred in 38 per cent. The total mortality rate was 10 per cent. The most characteristic roentgenographic manifestation is the triangular shadow with an axillary base. The treatment consisted of fresh air, good nutrition and hydrotherapy. Medication consisted of stimulants and expectorants. Camphorated oil was most frequently used. Inhalation of oxygen was used when necessary.

ROENTGEN DIAGNOSIS OF BRONCHOTETANY. O. GÖTTCHE, Arch. f. Kinderh. **85**:185 (Nov. 27) 1928.

A case is reported of a child, aged 2 years, who had marked expiratory dyspnea, respirations of 68 per minute, a pulse rate of 168 and a temperature of 37.1 C. (98.7 F.). The number of leukocytes was slightly increased, and there was a 14 per cent eosinophilia. The roentgenogram showed a marked density of the upper lobe of the right lung. Large doses of calcium were given, and the next day the symptoms had entirely disappeared. The roentgenogram was also normally clear. The author believes that in cases of bronchotetany the roentgenogram is characteristic. It shows a density like that in lobar pneumonia, but is not so sharply defined, resembling that in atelectasis more in this respect.

A CASE OF PURPURA FULMINANS. K. BOETTIGER, Arch. f. Kinderh. **85**:239 (Nov. 27) 1928.

The case reported was that of a girl, aged 4 years. The symptoms were extensive hemorrhages over both knee and ankle joints. The pulse and temperature were normal, as were the stools and the urine. The blood showed: hemoglobin, 40 per cent; red blood cells, 2,920,000; white blood cells, 48,700, and platelets, 21,600. Ten days later the hemoglobin had fallen to 34 per cent, and the hemorrhages had extended to the hips. A blood transfusion was done, and

the hemoglobin rose to 50, but the patient died three days later. Autopsy showed nothing particular except an anemia of the organs. A culture of the heart's blood was negative. The differential diagnosis included hemorrhagic diathesis, scurvy, hemophilia, the purpuras of Werlhof Schönlein and Henoch and the infections.

SANFORD, Chicago.

PATHOLOGIC CHANGES IN THE BONES IN INTESTINAL INFANTILISM. W. BAUMANN, Monatschr. f. Kinderh. **42**:5, 1929.

The author reports three cases of intestinal infantilism in which the osseous system showed changes typical of scurvy. These children received the juice of an entire lemon daily. In explanation, the author suggests that perhaps the vitamin of the lemon was destroyed in the intestine. As the children received spinach in addition, he rules out the idea that an insufficient quantity of vitamin was offered. He concludes that one must not lose sight of the old teaching that it is better to use raw milk than cooked milk.

BRONCHIAL ASTHMA. A. CZERNY, Monatschr. f. Kinderh. **42**:117, 1929.

A brief clinical description of bronchial asthma is given. The author expresses his conviction that food is not a factor, and his belief that the only certain origin is infection of the upper respiratory passages or psychic injury. Children are cured in the mountains, others at the seashore, others in the forest or in the country — any place that is favorable to healing of the respiratory infection.

In the diagnosis, the whistling râles are pathognomonic. The course of the disease — the occasional attacks and long intervals of health — somewhat resembles that of epilepsy, the author occasionally has found it associated with cardiac conditions but never with tuberculosis. It is sometimes confused with atypical whooping cough. Much more study of the disease is necessary.

CONTRACTED KIDNEY IN CHILDHOOD. F. EINECKE, Monatschr. f. Kinderh. **42**:130, 1929.

The author reports two cases of contracted kidney in childhood. One case was characterized by the typical symptoms of contracted kidney, namely, increased blood pressure, cardiac dilatation, increased nonprotein nitrogen and uremia. It seemed due to a generalized vascular disease, periarteritis nodosa. The second case was a typical juvenile arteriosclerosis.

CHRONIC INCREASED BLOOD PRESSURE IN CHILDHOOD. ERNST FAERBER, Monatschr. f. Kinderh. **42**:148, 1929.

A report is given of several cases of increased blood pressure associated with a hypertrophied heart and retinitis. In one case, observed for a number of months, all the symptoms, even the retinitis, disappeared. What the outcome will be, the author does not know.

LYMPHATIC REACTIONS IN CHILDREN. E. FEER, Monatschr. f. Kinderh. **42**:157, 1929.

In his experience during the last few years, Feer has seen a number of children with various diseases, showing typical lymphatic reactions in the blood. Seven of the patients had sore throat and a membrane, easily mistaken for those seen in diphtheria; eleven patients showed no sore throat and four had bronchitis and bronchopneumonia. Seven had various ailments.

In the diagnosis, great care must be taken to rule out diphtheria and lymphatic leukemia.

The author reports a case of chorea in which a hypnotic was used; leukopenia and a reduction of polymorphonuclears to 10 per cent occurred. He considers such a marked diminution of polymorphonuclears dangerous, and therefore recommends great care in the dosage. It should never be used for more than ten days or in doses of more than 0.3 Gm. per day.

THE USE OF PNEUMOTHORAX IN THE TREATMENT FOR PNEUMONIA. M. KLOTZ, Monatschr. f. Kinderh. **42**:312, 1929.

The author reports a clinical study of pneumonia in childhood in which he produced artificial pneumothorax according to the suggestions of Ibrahim and Duken. Good results were obtained in five cases; in many others, the treatment was not so successful.

THE INFECTIOUS DISEASES OF THE URINARY PASSAGES IN CHILDHOOD. H. VON METTENHEIM, Monatschr. f. Kinderh. **42**:338, 1929.

A review of the literature is given. The chief advances in knowledge of infectious diseases of the urinary passages in childhood have been in matters of technic, such as uroscopy and roentgenology. Not a great deal is known concerning etiology and pathogenesis. The rôle of the colon bacillus remains undetermined. In therapy, the majority of writers are quite skeptical. Rather than place confidence in drugs, they devote their skill to improving the general resistance of the infant and to offering sufficient quantities of fluid and food.

GERSTLEY, Chicago.

HYPERTHYROIDISM AND INSULIN SENSITIVITY. ERNST ADLER, Wien. Arch. f. inn. Med. **16**:342, 1929.

The author determined the sensitivity to insulin in fifteen cases of hyperthyroidism. Five units of insulin was injected, and repeated determinations of blood sugar were made over an experimental period. With such dosage, no essential difference was found between the normal and the pathologic cases.

Persons with mild or severe forms of hyperthyroidism did not react differently in their sensitivity to insulin. No essential difference was found between the basal metabolism and the insulin sensitivity.

SCHLUTZ, Minneapolis.

Nervous Diseases

ORGANIC NERVOUS DISEASE IN IDENTICAL TWINS. S. A. KINNIER WILSON and JULIAN M. WOLFSOHN, Arch. Neurol. & Psychiat. **21**:477 (March) 1929.

In health, homologous twins show a striking similarity of structural, functional and mental equipment. When organic nervous disease occurs in homologous twins, it is most probably the result of inherent defects and is always in both twins. The same obtains for the presence of anomalies and deformities in identical twins. An anomaly of development is always similar and equivalent in both homologous twins. Biologically considered, homologous twins are only one individual; physically they are two.

SANFORD, Chicago.

RESTLESSNESS IN INFANCY. HYMAN S. LIPPMAN, J. A. M. A. **91**:1848 (Dec. 15) 1928.

The hypertonic infant represents a distinct clinical entity, namely: hyperactivity and muscle strength, fussiness and restlessness, nearly continuous crying, vomiting and frequency of loose stools. The most commonly accepted theory is that of autonomic imbalance: either hyperactivity of the craniosacral division of the involuntary nervous system (consequently relieved by atropine) or hypo-activity of the thoracicolumbar division corrected by epinephrine. Whereas, according to the behavioristic theory, the phenomena of hypertonicity are conditioned by postnatal environmental factors such as feeding and the emotional attitudes of the patients, instability of the involuntary nervous system is usually demonstrable at birth. This paper represents a study of sixty-three infants with symptoms of colic, vomiting and restlessness. As a result of the investigation, the following suggestions are offered to control restlessness in infancy: Every effort should be directed to insure

for the mother rest and relaxation in a peaceful environment. The greater share of the care of the infant should be turned over to persons other than the parents. Frequent dietary changes should be instituted until the ideal food or schedule can be realized. Every reliable means of relieving the swallowing of air should be utilized. The infant should be placed at the breast while he is in a drowsy state, and the use of chloral hydrate must be considered. One should use atropine, increasing the dosage to a point of tolerance before deciding that its action is ineffectual.

BONAR, Salt Lake City.

SOME OBSERVATIONS IN CONNECTION WITH EPILEPSY AND SOME OF THE DISEASES OF CHILDHOOD: A REPORT BASED PRIMARILY ON LABORATORY FINDINGS SUPPLEMENTED BY A SCRUTINY OF THE PERSONAL HISTORY. HAROLD A. PATTERSON and SAMUEL M. WEINGROW, New York State J. Med. **28**:1106 (Sept. 1) 1928.

A study was made in the Craig Colony laboratory to determine whether examination of the blood of epileptic persons would show any changes that could be attributed to the various diseases of childhood which the patient had had. One hundred and fifty patients at Craig Colony were examined, and no relationship was established between epilepsy and these diseases. In this series, the patients with a history of whooping cough had a more severe form of epilepsy than others.

In epilepsy, the coagulation time is accelerated. There is a tendency to lymphocytic leukocytosis, and eosinophilia is possible.

AIKMAN, Rochester, N. Y.

THE NERVOUS CHILD IN OUR MIDST. BERNARD MYERS, Practitioner **122**:80 (Feb.) 1929.

The nervous child is one who is capable of intense emotion, which can be quickly aroused and over which he has insufficient control. He is possessed of restless energy, but tires easily. Difficulties seem greater to him than they really are. He is worried by trifles and is usually timid. Many such children are "show-offs." Negativism is a prominent symptom. Neurotic children frequently have prepossessing ways. They easily become pets of the family and appeal strongly to strangers. An unstable vasomotor system frequently is present, along with hypersensitiveness of the senses, particularly touch. Night terrors, enuresis and phobias are frequent accompanying symptoms. Many neurotic children attain distinct success in the arts if possessed of the necessary industry and staying power. Others become failures in one thing after another.

Diminished blood calcium and increased cholesterol have been found consistently in neurotic children.

In an acute illness, unless it is severe, the nervous child is a great trial to the practitioner. If no notice is taken of the child, if the nurse is suitable and if the mother is not in the room, the examination may proceed without undue trouble.

Neurotic children should be sent to school because self-control, companionship, etc., may be secured only in this way.

The mother is generally neurotic; she must therefore learn self control in order to place her child in the correct environment. If this is impossible, the child must be sent away to a friend, a relative living in the country or, at a suitable age, to a good boarding school.

A spirit of cooperation with the child, in order to secure his confidence, is the only method of working with him. The method employed at one time of placing nervous children in a dark room, and semi-starving, threatening and whipping them was extremely harmful.

The majority of the peculiarities of the nervous child have nothing to do with sex, and to imply otherwise might result in much harm.

BARRETT, San Francisco.

INVOLUNTARY MOVEMENTS OF ARM: PSYCHONEUROSIS. J. D. SLIGHT, Proc. Roy. Soc. Med., October, 1928.

A girl, aged 15 years, had had involuntary movements of the right upper extremity for more than ten years. At 2 years of age, she had her left middle finger injured and consequently amputated. Not until she was sent to school was it found that she could not keep her right hand steady. The movements gradually became worse until they were noticed to extend to the face on several occasions. Further details are given in the report.

WILLIAMSON, New Orleans.

CONGENITAL HYDROCEPHALUS WITH MALFORMATIONS. BABONNEIX and ROUECHE, Bull. Soc. de pédiat. de Paris **26**:313 (June) 1928.

A boy, aged 14½ years, showed obesity, polydactylism, an increase in the number and extent of the mastoid cells (roentgenologic examination), blocked foramina of Luschka and Magendie and diminished pressure of the fluid at lumbar puncture. He carried his head to the left; the gait was unsteady, and he kept his feet wide apart. The occipitofrontal circumference was 59 cm.

A CASE OF BILATERAL EXTENSOR PARALYSIS OF THE THREE OUTER FINGERS AND CERVICAL RIBS. JEAN HALLE and LEON BABONNEIX, Bull. Soc. de pédiat. de Paris **26**:316 (June) 1928.

The third, fourth and fifth fingers of the right hand in a boy, aged 11 years, showed absolute loss of movement to the right, and impaired movement to the left. The lumbricalis and interossei movements were intact, and the extension of the two terminal phalanges on the first was retained. There were no trophic or vasomotor disturbances, and the reflexes were normal. The electrical reaction showed partial degeneration of the extensor digitorum communis to the third and fourth, and of the extensor proprius to the fifth fingers. Sensation was normal. Roentgenologic examination was inconclusive, possibly indicating a small cervical rib at the level of the seventh cervical vertebra. The author mentions that a relationship does not necessarily exist between the size of the cervical rib and the severity of the pathologic phenomena.

THE CHVOSTEK SIGN IN OLDER CHILDREN. MARIE NAGEOTTE-WILBOUCHEWITCH, Bull. Soc. de pédiat. de Paris **26**:358 (July) 1928.

In thirty children of from 4 to 16 years of age, the Chvostek sign was present in 14 per cent. There were nervous and physical defects in the children with a positive sign or in their ancestors or in both, and the author draws the conclusion that the sign occurs in children who are defective, either personally or hereditarily. The figures here are lower than those in other series reported, which may be due to a difference of country as well as in the way of eliciting the sign.

MENINGITIS DUE TO PFEIFFER'S BACILLUS: VEGETATIVE ENDOCARDITIS WITH ANATOMIC AND BACTERIOLOGIC STUDIES. H. GRENET DE PFEIFER and R. LEVENT, Bull. Soc. de pédiat. de Paris **26**:358 (July) 1928.

A boy, aged 19 months, was taken acutely ill, with severe toxemia, bronchitis, diarrhea and meningitis, the signs of the latter developing late; arthritis of the left knee developed two days before death, which took place twenty-eight days from the onset of the illness. The spleen became palpable, and auscultation revealed a gallop rhythm three days before death. Autopsy showed diffuse purulent meningitis and vegetative endocarditis as the essential anatomic lesions. Pfeiffer's bacillus was found in the spinal fluid removed during life; blood culture produced no growth. Articular fluid removed from the left knee at autopsy, and culture made from the heart's blood in the agonal state produced a bacillus which was identified as *B. paratyphosus* B. The author discusses the possible responsibility of Pfeiffer's bacillus for the entire pathologic changes, and cannot determine what rôle *B. paratyphosus* played.

BENJAMIN, Montreal.

MENINGEAL REACTION IN AN INFANT DUE TO PROLONGED EXPOSURE TO THE SUN. A. BÉRAUD, Bull. Soc. de pédiat. de Paris **26**:526 (Dec.) 1928.

A girl, aged 5½ months, who had been restless for several days developed a temperature of 39.2 C. (102.5 F.). The fontanel was decidedly full. The child had been accustomed to remain alone for long periods in the sun, and all the exposed areas of its body were deeply tanned. Cooling baths, small enemas and protection from the sun quickly relieved the symptoms. After the child was taken for a ride in a covered baby carriage, the symptoms all returned with increased severity. The cerebrospinal fluid contained an abnormal amount of albumin and 55 cells, 90 per cent of which were lymphocytes. Complete recovery ensued; the child was well at 2 years of age. The author believes that infection can be excluded as the cause of the meningism. He attributes the condition to isolation, probably to the heating effect of the sun rather than to the ultraviolet rays.

CONVULSIONS IN AN INFANT FIFTEEN MONTHS OLD FOLLOWING THE INJECTION OF LARGE AMOUNTS OF CAMPHORATED OIL. A. BÉRAUD, Bull. Soc. de pédiat. de Paris **26**:532 (Dec.) 1928.

A dystrophic infant, weighing 6 Kg. at the age of 15 months, received from another physician injections of 5 cc. of 10 per cent camphor in oil every other day. Convulsions and coma followed the fifth injection. The cerebrospinal fluid contained a reducing substance corresponding to 160 mg. of dextrose per hundred cubic centimeters. Béraud thinks that this substance may have been glycuronic acid.

CLAUSEN, Rochester, N. Y.

HYPOTONIA IN INFANTS. H. LENAIRE and DESBUQUOIS, Nourrisson **17**:28 (Jan.) 1929.

Chronaxia is inversely proportional to the muscular tone. Section of the posterior roots produces hypotonia, indicating that tonus is a reflex action of peripheral origin and consummated through the medium of the spinal cord. It is also known that section of the cervical cord or section of the rami communicantes can also produce a marked hypotonia.

Attempts to explain the two types of muscular contraction have led some authors to hypothesize that the clonic contraction is due to the action of the striated fibers which are controlled by cerebrospinal nerve centers and that tonicity resides in the sarcoplasm which is innervated from the sympathetic nerve. Pieron feels that it is necessary to distinguish between the tonus of resting muscle (sympathetic control) and the tonus of coordinated muscular movement (cerebrospinal control). Luciani insists on the rôle of the cerebellum and Dieter's nucleus. The maintenance of muscular tone involves a complex mechanism. Exaggerated forms of both hypertonia and hypotonia require no demonstration. In cases of lesser severity, the degree of tonicity or atonicity requires mensuration. This can be done by placing the infant on a hard flat surface, with one leg extended and the other flexed; first, the thigh is flexed on the pelvis and then the leg on the thigh. The angle which the long axis of the thigh in extreme flexion makes with the horizontal is called the crural angle and is normally about 10 degrees. The angle which the long axis of the leg makes when extended to the horizontal is called the popliteal angle and is normally about 90 degrees at full flexion.

During the first three months of life, there is a physiologic hypertonicity. This hypertonicity is not associated with a shortened chronaxia. At the age of 18 months, a physiologic hypotonia is present, which disappears when the child is 2 years of age.

A transitory hypotonia is frequently seen in certain toxi-infectious syndromes with acetonemia and dehydration; it is also seen at the end of and during convalescence from many acute infections, and in the pseudoparalyses of Parrot and Barlow. The persistent hypotonia is found in rickets, in myatonia congenita (Oppenheim and Forster) and in some of the infantile encephalopathies (mongolism, amaurotic family idiocy and hydrocephalus).

MCCLELLAND, Cleveland.

HEMORRHAGIC HYDROCEPHALUS DUE TO EPENDYMITIS. MAMERTO ACUÑA and MARÍA TERESA VALLINO, Arch. latino-am. de pediat. **22**:741, 1928.

The authors report a case of hemorrhagic encephalitis in an infant, aged 22 days, in whom the condition was apparently due to ependymitis.

There had been no history of infection in the case. No organisms were found in the cerebral fluid. There were no evidences of syphilis. The parents showed negative Wassermann reactions.

SCHLUTZ, Minneapolis.

CONGENITAL MYATONIA: A HEREDITARY DEGENERATIVE DISEASE. G. KATZ, Arch. f. Kinderh. **85**:161 (Nov. 27) 1928.

Katz reports the cases of two infant brothers with congenital myatonia. He asserts that in most cases the disease may be traced and proved to be present in several members of the same family. Clinical, pathologic and anatomic investigations in these two cases and a study of the literature show that congenital myatonia should be considered a heredodegenerative disease of the central nervous system. The cause is not yet known, but the disease originates in an atrophy of the nerve tracts, determined in the germ plasm. Toxic, metabolic and infectious influences may result in atrophy, degeneration and absorption of the anterior cornu cells, the peripheral nerves and the nerve endings. Abiotrophy in the segments of the trophic nerve tracts varies in individual cases and is sometimes more spinal in the anterior cornu cells, sometimes more peripheral in the nerves, and sometimes in the nerve endings. The prognosis varies according to the degree and extent of the disturbances and degenerations. In cases of extensive congenital myatrophy it is unfavorable, and death occurs generally in the first or second year from respiratory disease. Even in more benign forms of myatonia, improvement is rare, while recovery has never been reported. Therapy consists primarily in preventive measures against infections of the respiratory tract; all disturbing influences should be kept away from the patient. Katz considers that the name, therefore, is inappropriate and would prefer to term the condition congenital muscular atrophy. This observation is important, since Oppenheim's disease has not been considered as hereditary.

SANFORD, Chicago.

ENCEPHALITIS INTERSTITIALIS CONGENITA VIRCHOW. A. BERKHOLZ, Monatschr. f. Kinderh. **42**:12, 1929.

Under the title of congenital interstitial encephalitis, in 1865, Virchow published the report of a number of cases in which the central nervous system of the newborn infant was studded with areas of cells showing fatty degeneration of the nuclei. A number of later observers have claimed that this not a definite disease but that it is a result of injuries or asphyxia during birth. The author reports seven instances of death in new-born children in whom these observations were made. The cases occurred in families, in each of which three children were lost immediately after birth. The observations at autopsy were typical. In view of this familial tendency, the author concludes that the disease is a separate clinical entity. Premature infants are particularly susceptible to it.

FURTHER CONSIDERATIONS IN THE RECOGNITION OF OCCULT HYDROCEPHALUS. JOHANN VON BOKAY, Monatschr. f. Kinderh. **42**:109, 1929.

The author reports four cases of microcephalus in which autopsy showed a typical hydrocephalus. He reports a fifth case in which by means of ventriculography, a spina bifida occulta was also found to exist. Hydrocephalus was always the dread of surgeons who operated on patients with spina bifida, but they considered it a complication of the operation. This study shows that it may be a coexisting condition. The best clinical evidence of hydrocephalus is a persistence of the fetal fontanels and sutures. If these are present, an operation for spina bifida should not be attempted before further studies are made.

GERSTLEY, Chicago.

Diseases of the Ear, Nose and Throat

THE INCIDENCE OF NASAL SINUSITIS WITH DISEASES OF THE EAR: ONE HUNDRED CASES IN CHILDREN. EDMUND PRINCE FOWLER, Arch. Otolaryng. **9:** 159 (Feb.) 1929.

One hundred consecutive cases were studied to determine the relationship between acute nasal sinusitis and diseases of the ear. Complete histories were taken; otorhinoscopic, functional, audiometric for both air and bone conduction, and stereorentgenographic tests were made. Children were studied, especially with the aim of preventing later disease by therapeutic and prophylactic treatment.

Five cases of nonsuppurative otitis media, fifty-seven of suppurative otitis media in which healing had occurred, thirty-four of recurrent suppurative otitis media, thirteen of chronic suppurative otitis media and eleven of nerve deafness were found in the group. Fifty-seven per cent showed moderate or severe nasal sinusitis, 71 per cent had pathologic changes in the ethmoid septums, and in 86 per cent of the cases of deafness there were at least some positive signs of involvement of the sinuses. This does not necessarily mean that sinusitis caused the deafness in all cases but rather that the conditions are closely related and that infection in each location may cause it in the other. To quote the author, "I wish to stress especially the importance of sinus disease as the cause of recurrence and chronicity in suppurative otitis and progressive deafness therefrom." He states his belief that true otosclerosis may be caused in part by continued present and adjacent infection of the ear. It is the end-result of previous disease. Therefore, the prevention and cure of disease in the ear involves care of the sinuses, and prevention and cure of diseases of the sinuses must often mean care of the ears.

GRADENIGO'S SYNDROME. SAMUEL D. GREENFIELD, Arch. Otolaryng. **9:** 171 (Feb.) 1929.

Gradenigo's syndrome is caused by the extension of an acute otitis into the petrous tip of the mastoid, thus causing a local circumscribed serous leptomeningitis over the involved bone. Pressure from the edema on the sixth (most often), third and fourth nerves causes the paresis seen in these cases; the temporoparietal, supra-orbital and retrobulbar pain results from pressure on the gasserian ganglion. Most of the reported cases have been in those in whom a rather massive mastoiditis exists. If the patient's resistance is not great enough to keep the process localized, a general meningitis results. If it does not spread, complete recovery is the rule.

An interesting case report of a child, aged 6 years, is given.

THE TREATMENT OF ACUTE INFECTIONS OF THE MIDDLE EAR AND PREVENTION OF MASTOIDITIS. ADOLPH I. SCHWARTZ, Arch. Otolaryng. **9:** 185 (Feb.) 1929.

Of 1,200 patients with infection of the middle ear treated by the author, only 19 were operated on for mastoiditis. The condition in all of these 19 patients was, in one way or another, unfavorable for this form of treatment.

The method used is a suction produced by a rather simple apparatus for the purpose of draining the pus from the middle ear and reducing the pressure in the vault caused by swelling and formation of pus. For this purpose, an incision is made in the drum membrane before the suction is applied.

This treatment should only be used in the early stages before there is tenderness at the tip of the mastoid process and before the cells are involved.

BARNETT, Chicago.

RETROPHARYNGEAL LYMPHADENITIS AND ABSCESS. HERMAN B. SHEFFIELD, M. J. & Rec. **29:**26 (Jan. 2) 1929.

Owing to the tendency of the lymph nodes to atrophy in children over 3 years of age, retropharyngeal lymphadenitis is most common among infants. Many cases of severe rhinitis are in reality mild forms of lymphadenitis. This applies also to children more than 3 years of age. The onset is generally slow and insidious. It is

frequently associated with grip, measles and the like, which explains its occasional occurrence in epidemic form. In the group of cases in which suppuration sets in, the symptoms of lymphadenitis having escaped observation, the temperature rises (from 103 to 105 F.). Marked enlargement of the glands in the neck, torticollis, loud snoring with the mouth wide open, dysphagia, possibly considerable dysnea, a croupy cough and, sometimes, aphonia are present. On examination of the pharynx, the abscess can be seen and felt. The structure of the retropharyngeal space and the treatment for lymphadenitis are given.

WILLIAMSON, New Orleans.

THE PROGNOSIS IN MASTOID DISEASE. E. WATSON WILLIAMS, Practitioner **112**:36 (Jan.) 1929.

1. Primary mastoid disease is especially prevalent during early life and is not rare even in nurslings.

2. The mortality in mastoid disease is largely the result of delay in treatment, and is therefore preventable. Sigmoid sinus thrombosis is the most frequent of fatal complications.

3. Apart from existing complications, practically the only operative risk is that of the anesthetic.

4. A dry ear and good or at least fair hearing should result from operation in almost every case of primary acute mastoid disease suitable for the Schwartze operation.

5. Operation should result in a dry ear in 80 per cent of the cases of chronic mastoid disease. When the Schwartze operation is suitable, the same proportion of patients should have at least fair hearing.

6. After the radical operation, good hearing is the exception; 80 per cent of the patients should have dry ears, while actual otorrhea is unusual. In many cases, one can expect a material gain in general health as well as relief of local symptoms.

7. Associated disease of the nose and nasopharynx is frequent and requires treatment.

AUTHOR'S SUMMARY.

VINCENT'S ANGINA. M. OLINTO, Arch. de pediat. Brazil **1**:18 (Oct.) 1928.

In the cases described, the membrane and the clinical picture resembled those in diphtheria, but no results were obtained with antitoxin. The optimal treatment was 0.2 Gm. of arsphenamine.

SANFORD, Chicago.

THE HANDWRITING OF PERSONS WITH SPEECH DISTURBANCES. K. ROMÁN-GOLDZIEHER, Ztschr. f. Kinderforsch. **35**:116 (Jan. 30) 1929.

The handwriting of stutterers and stammerers shows peculiarities (ataxia, hyperdynamic features, frequent repetition of letters, etc.) which are characteristic of this disease and which are always present unless compensated for.

REICHLE, Cleveland.

Diseases of the Skin

ACRODYNIA WITH MULTIPLE GLANDULAR ENLARGEMENT. R. DEBRÉ, MLLE. HÉBERT and GARDINIER, Bull. Soc. de pédiat. de Paris **26**:509 (Dec.) 1928.

To the already complex picture of acrodynia, the authors add enlargement of all the superficial lymph nodes, observed in an infant, aged 6 months.

PRURIGO-STROPHULUS, ASTHMA AND DYSPEPSIA CAUSED BY CEREALS. R. MATHIEU, Bull. Soc. de pédiat. de Paris **26**:519 (Dec.) 1928.

The author believes that too much stress has been laid on animal proteins as a cause of prurigo. He cites fourteen cases in which the stools gave evidence of fermentation, increased acidity and failure to digest starch. By giving the patients

milk, eggs and meat and by excluding potatoes and legumes from the diet, he often obtained excellent results. He cites the case of a man, aged 40, who had suffered for twenty years from hay-fever, and who had restricted his own diet almost entirely to cereals. The stools were bulky and acid. A diet rich in protein and in animal fats, with restriction of potatoes and legumes, was followed by the absence of symptoms ordinarily occurring from June to October. No skin tests were mentioned, nor were any failures cited.

CLAUSEN, Rochester, N. Y.

THE RELATION OF DESQUAMATIVE ERYTHRODERMIA AND EXUDATIVE DIATHESIS. M. RUTHARDT, Arch. f. Kinderh. **85**:221 (Nov. 27) 1928.

In thirteen children with erythrodermia, only two, or 22.5 per cent, showed exudative diathesis to a marked degree, and one had only slight symptoms. In testing children with the McClure and Aldrich test, the author found that the disappearing time was a little shorter than normal in five children with erythrodermia, and that in five cases of exudative diathesis it was also decreased.

SANFORD, Chicago.

PIGMENTATION OF THE SKIN FOLLOWING THE USE OF IRRADIATED ERGOSTEROL. J. BERNHEIM-KARRER and G. ZARUSKI, Monatschr. f. Kinderh. **42**:24, 1929.

In an experiment on twins in which one was given irradiated ergosterol, it was found that after two months this child developed a decided pigmentation of the skin while the untreated child did not. A small piece of skin was excised, microscopic examination showed that the pigment in the basal layer of the epidermis was considerably richer than that in the untreated child. No explanation is offered.

CLINICAL OBSERVATIONS ON HERPES IN EARLY CHILDHOOD. HELENE ELIASBERG, Monatschr. f. Kinderh. **42**:139, 1929.

Herpes simplex can occur in early childhood. It may appear in epidemics, both as the simple type or the one associated with varicella. The fact that during attacks of recurring herpes, patients have typical varicella shows that the two conditions are not identical. The localization on all parts of the skin and mucous membrane in infants is like that in the adult. Herpes is frequently associated with phlyctenular conjunctivitis, a fact which leads the author to suspect that some cases of the latter may really be cases of herpes.

DERMATITIS EXFOLIATIVA AND ERYTHRODERMIA DESQUAMATIVA. CARL LEINER, Monatschr. f. Kinderh. **42**:331, 1929.

In a report of a case, the writer reemphasizes his frequent observation that erythrodermia desquamativa is a definite clinical entity and should not be confused with the other dermatoses of the new-born infant.

GERSTLEY, Chicago.

Surgery and Orthopedics

THE TREATMENT OF BURNS AND SCALDS BY TANNIC ACID. GERTRUDE HERZFELD, Practitioner **122**:106 (Feb.) 1929.

In considering the treatment for burns and scalds, one aims at the following: (1) prevention of absorption from the injured tissues; (2) prevention of local sepsis; (3) painless dressing or covering for the burned area; (4) rapid healing with a minimum of scar formation.

All these aims are ideally met by tannic acid. A freshly prepared 2.5 per cent solution is applied over the burned area by means of a spray. The patient is then covered with a cage in which an electric light bulb is placed to maintain body warmth. The spray is repeated every hour until the coagulum appears;

then nothing further is required in the way of dressings. The coagulum separates of its own accord in from seven to ten days. Should sepsis occur, the coagulum must be completely removed before the application of wet dressings.

If previous treatments have been given, this method should not be applied for more than twelve hours; also, no coagulum will form after from twenty-four to thirty-six hours.

By the use of this method, the mortality in children has dropped from 38 to 9 per cent. This alone justifies its adoption.

BARRETT, San Francisco.

TREATMENT OF PURULENT PNEUMOCOCCIC PLEURISY. TIXIER and DESEZE, Arch. de méd. d. enf. **32**:20, 1929.

Reporting a case of bilateral empyema in a boy, aged 8, the authors discuss the various methods of treatment, and make a plea for what they term nonprecipitant management. The patient had an invasion of lobar pneumonia in the left lung, which continued for the classic period of nine days and subsided by lysis. After two days, empyema developed at the base of the left lung; a radical operation was performed five days later. Free drainage, however, did not ameliorate the symptoms; high temperature with great prostration and loss of weight supervened until a more careful examination revealed a new area of consolidation under the right clavicle. On the eighth day the temperature fell by crisis, and the child seemed to be entering the period of convalescence; on the following morning, however, a persistent cough appeared, with fever, and a second accumulation of pus was found, this time at the base of the right lung. As the left pleura was still discharging freely and the right side of the chest filling rapidly, it was decided to allow the latter to remain closed and to free the cavity by fractional aspiration. The first thoracentesis released 360 cc. of a thick pneumococcic pus, and subsequent punctures, twenty-four hours apart, increased this amount to 500 cc. After each aspiration, an intrapleural injection of 20 cc. of a filtered pneumococcic culture was given. After twenty days, when the patient seemed quite comfortable and restoration was well under way, the right pleural cavity again filled rapidly. The pleurotomy wound on the left side having healed, the right side was subjected to a similar operation; drainage ceased on the eleventh day thereafter.

The clinical argument advanced is one of watchful waiting; the medical attendant is urged to temporize, in frank cases of pneumococcic pleurisy, until the abscess is well walled off and the pulmonary inflammation has subsided.

AMESSE, Denver.

ABSCESS OF THE HIP JOINT COMMUNICATING WITH THE INTESTINE. M. ROEDERER, Bull. Soc. de pédiat. de Paris **26**:375 (July) 1928.

The patient, aged 14 years, was first seen three years before the paper was written with disease of the hip; after about a year under observation, he developed an abscess which was drained on two occasions and which discharged through two fistulas where the openings had been made. On culture the pus showed staphylococci, streptococci and *B. coli*. The patient passed gas through the fistulas as well as by rectum. Injections of iodized poppy seed oil 40 per cent followed the course of the large bowel and sigmoid flexure. There was severe toxemia before drainage was established by the incisions, but no abdominal symptoms; the stools were normal.

BENJAMIN, Montreal.

PROLONGED FEEDING BY DUODENAL TUBE IN A CASE OF GASTROSTOMY WITH PHAGODENIC ULCER OF THE ABDOMINAL WALL. H. L. ROCHER and DAMADE, Bull. Soc. de pédiat. de Paris **26**:538 (Dec.) 1928.

In a child, aged 34 months, lye burns caused stricture of the esophagus which was treated by gastrostomy and dilatation. As the gastric contents had produced a serious ulcer of the abdominal wall, and the child's weight had decreased, he was fed through an Einhorn tube, kept in place for two months. The authors

express their belief that this treatment put the stomach at rest and, by relaxing the esophageal spasm, assisted in the success of dilatation.

CLAUSEN, Rochester, N. Y.

Miscellaneous

PHYSIOLOGIC CHANGES IN POSTURE DURING THE FIRST SIX YEARS OF AGE. CLIFFORD SWEET, RICHARD GWYN WATSON and HENRY E. STAFFORD, J. A. M. A. **91**:1519 (Nov. 17) 1928.

The health of the growing child is determined by heredity, nutrition, infection and posture. Each child passes through a definite and predicated racial biologic postural development. While postural tendencies are of a hereditary nature, postural development during growth is influenced by such factors as nutrition, infection, shoes, clothing, bed, habits of walking and standing and sitting, and muscle training. Certain postural changes are incident to the age of the person and tend to return to a more desirable state if not interfered with.

BONAR, Salt Lake City.

SOME FACTORS IN THE INFANT MORTALITY PROBLEM. CHARLES HERMAN, New York State J. Med. **28**:1087 (Sept. 1) 1928.

In 1927, the death rate for infants under 1 year of age in New York was less than fifty-six per thousand births. In the borough of the Bronx with 1,000,000 inhabitants, the rate was less than forty-one per thousand.

The mortality curve has shown a marked change, and the highest point is now reached in the spring. Summer shows the lowest rate. The reduction in the mortality rate is due to an improved milk supply and the education of mothers in regard to infant feeding and hygiene.

Respiratory infections have not been controlled to any extent, and there has been little or no reduction in deaths in early infancy.

AIKMAN, Rochester, N. Y.

THE USE OF THE TERM VACCINATION AND THE NECESSITY OF SPECIFYING IT IN PUBLIC HEALTH WORK; REGISTRATION OF THE VARIOUS PROCESSES OF IMMUNIZATION. YVONNE POUZIN-MALEGUE, Bull. Soc. de pédiat. de Paris **26**:322 (June) 1928.

To avoid confusion regarding the various methods of immunizations now practiced, the term "smallpox" should always accompany "vaccination." Furthermore, an official record of immunization against smallpox, diphtheria, tuberculosis and other diseases should be kept of every child. Until such a method is adopted, it is suggested that printed forms be sent out to be pasted in the family register and properly filled in at the time any process of immunization is done.

ANURIA DUE TO MEDICATION IN AN INFANT. YVONNE POUZIN-MALEGUE, Bull. Soc. de pédiat. de Paris **26**:325 (June) 1928.

A girl, aged 20 months, showed anuria of fifty hours' duration (during the first forty hours the condition was observed only by the mother), without diarrhea, vomiting, excessive perspiration or any other symptoms. This was thought to be due to suppositories, each containing thymol, 0.02 Gm., and naphthalene, 0.012 Gm., in cocoa butter, given daily for eighteen consecutive days previous to the onset of the anuria.

BENJAMIN, Montreal.

COMMISSION OF THE SOCIETY OF PEDIATRICS ON SOCIAL HYGIENE AND SOCIAL AID. M. LESNÉ and M. J. HUBER, Bull. Soc. de pédiat. de Paris **26**:548 (Dec.) 1928.

This article is a report of the recommendations made to the Administration de l'assistance publique.

CLAUSEN, Rochester, N. Y.

EUGENICS. E. JORDAN, Nourrisson **17**:20 (Jan.) 1929.

The proponents of eugenics advance two propositions for improving the human race: (1) the prevention of undesirable persons from procreating their kind and (2) encouragement of the better element to increase and multiply.

Progress along either path is easy for the breeder of animals, but is difficult for the guardian of human destiny. Prevention of procreation can be assured only by means of sterilization, which can be exacted only from the veriest pariahs of society: the vicious or confirmed criminals and the hopelessly insane. The great mass of undesirables, unfit and indigent, remains untouched. From the positive side, one encounters equal difficulties. Who will be the arbiter to decide which qualities should be fostered and which should be condemned? Shall the physical be given precedence over the moral and spiritual? Supposing a decision can be reached, how can procreation be constrained in those possessed of superiority? Such selectivity must arrive at the same goal as malthusianism, and the cycle becomes a vicious one without accomplishing its original purpose; the birth rate is lowered until finally selectivity becomes impossible through lack of numbers. Natural and spontaneous selection preserves and improves the race without imposing unpleasant and impossible restrictions.

McCLELLAND, Cleveland.

THE HISTORY OF PEDIATRICS IN BRAZIL. O. DE OLIVEIRA, Arch. de pediat. Brazil **1**:1 (Oct.) 1928.

Professor Oliveira discusses the development of pediatrics in Brazil.

THE ASPECT OF PEDIATRICS IN RIO DE JANEIRO. F. FIGUEIRA, Arch. de pediat. Brazil **1**:8 (Oct.) 1928.

The peak of gastro-intestinal diseases in Rio de Janeiro comes in the winter. The heaviest mortality from diarrhea and enteritis comes in November, December and January. Rickets does not exist to a great extent. The rate of congenital syphilis and tuberculosis is rather high. In one clinic it was estimated that from 25 to 28 per cent of the infants had clinical symptoms of syphilis, and 20 per cent of the infants gave positive reactions to the Pirquet or Mantoux tests.

SANFORD, Chicago.

VENOUS PUNCTURE IN THE NURSLING. MARIA LUISA SALDUN, Arch. latino-am de pediat. **22**:698, 1928.

In 250 consecutive venous punctures, failure is recorded in 14 cases. Puncture of the longitudinal sinus is an easy and entirely safe procedure if proper precautions are taken. It is contraindicated if there are eczematous eruptions about the head or any area of pyodermia, on account of the danger of secondary infection.

Before injecting solutions or serums, it is well to aspirate a little blood to make sure that the lumen has been entered. Puncture of the jugular vein, although not as easy as that of the longitudinal sinus, is safer and should be given preference over the former.

SCHLUTZ, Minneapolis.

THE NEW CHILDREN'S HOSPITAL AT BASEL. E. WIELAND, Arch. f. Kinderh. **85**:248 (Nov. 27) 1928.

A detailed description and the plans of the newly built children's hospital are given.

SANFORD, Chicago.

PROCEEDINGS OF THE GERMAN PEDIATRIC SOCIETY. Monatschr. f. Kinderh **41**:464, 1928.

The proceedings of the German Pediatric Society for 1928 are contained in the December issue of the *Monatschrift für Kinderheilkunde*. The January issue of 1929, delivered at the same time, is published as a Festschrift in honor of the sixtieth birthday of Arthur Keller.

About thirty articles appeared in the December issue, and more than forty in that of January. Whether the January issue is part of the proceedings of the German Pediatric Society is not indicated. In the December issue are also the proceedings of the German Infant and Child Welfare Association with special reference to the high mortality of early infancy.

The session opened with a number of papers on child psychology. Then came reviews of the general subject of water metabolism. The subject of pneumonia was discussed, Ludwig F. Meyer giving a thorough review of the various clinical types and their treatment. He has nothing new to offer in therapy but hopes that something will result from the American serum. The roentgenologic diagnosis of pneumonia was carefully considered by Duken.

It is refreshing to note that pediatricians are at last taking an active interest in the physical makeup of the children's hospital. Excellent papers were read by Feer, Noble and Pirquet, Schlossmann, Bessau and others.

Some articles were of special interest. Nitschke demonstrated an active extract of the thymus gland. Mautner gave a thorough review of water metabolism. Stahlberg, by using the refractrometer, showed that the blood protein is considerably higher in tuberculous pneumonia than in lobar pneumonia or bronchopneumonia.

In the Infant Welfare section, papers by Rott, Kustner, Thomas, Langer and Coerper dealt mainly with the prevention of injuries at birth and prematurity.

THE CONSTRUCTION OF A CHILDREN'S CLINIC. W. BIRK, Monatschr. f. Kinderh. **42**:33, 1929.

The author describes in great detail the construction of a children's clinic.

THE TRANSMISSION OF INFECTION IN CONTAGIOUS WARDS. WILHELM KNOEPFELMACHER, Monatschr. f. Kinderh. **42**:318, 1929.

The article contains a diagram of Knoepfelmacher's wards for contagious disease and gives the results of his method of quarantining his patients. He was able to prevent the spread of scarlet fever from cubicle to cubicle. Diphtheria likewise was not transmitted except in certain cases in which the infection was traced to physicians and nurses who were carriers. Measles was fairly well controlled, with only 7 cases of contagion among 120 patients. Neither the isolation of the patients in cubicles nor the wearing of masks by the nurses prevented the spread of chickenpox. The author expresses the opinion that the only way to combat chickenpox is by having a separate air intake and exhaust in the isolation chamber. The fact that many inexperienced nurses did not develop contagious disease suggests that face masks may be of value.

GERSTLEY, Chicago.

Society Transactions

NEW YORK ACADEMY OF MEDICINE, SECTION OF PEDIATRICS

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STAFFORD MCLEAN, M.D., *Presiding*

BERIBERI IN LATE INFANCY; THE RESULT OF CELIAC DISEASE. Dr. SIDNEY V. HAAS.

Beriberi can occur in any climate. It occurs in early childhood in the temperate zone, although heretofore it was mostly unrecognized.

A study of celiac disease reveals in some of the severe cases the presence of all the classic symptoms of beriberi: edema, pallor, dyspnea, cardiac dilatation, paresthesias, weakness, irritability and paralyses.

Five cases of celiac disease complicated by symptoms of beriberi are described.

A number of writers have considered celiac disease due to avitaminosis B; others have considered the avitaminosis to be secondary in celiac disease. A short history of infantile beriberi is given. Cases arising in celiac disease among older infants conform more nearly to the adult type.

Beriberi is due to the absence of vitamin B from the diet. Celiac disease is characterized by an inability of the organism to utilize carbohydrates which are the chief carriers of vitamin B. The end-result in either case is the same whether vitamin B is not ingested or whether it is not absorbed.

The pathologic changes in beriberi and celiac disease are the same, except that in beriberi nerve degeneration has been frequently demonstrated, while there is no report available of any case of celiac disease in which the nerves have been examined. The presence of paralyses in the latter disease makes it probable that examination of the nervous system would reveal such degeneration.

The symptoms are almost identical except that constipation is common in beriberi, while diarrhea is common in celiac disease. Cardiac symptoms are often prominent in beriberi, while they are not prominent in celiac disease. Tables showing the symptoms and the results of pathologic examinations illustrate this.

The response to the addition of vitamin B to the diet (in the present study, bananas were given in large amounts) is prompt and striking and is similar to the response to appropriate treatment in beriberi.

In both conditions the depression, asthenia, edema and oliguria clear up at once and the paralyses later. The anemia is slow in disappearing. If these were cases of ordinary beriberi, this would mean a cure; but although the symptoms enumerated are all corrected, the inability to utilize carbohydrates and fats and the protuberant abdomen continue much longer.

For a long time, the resemblance of cases of celiac disease to the published description of beriberi made it seem probable that celiac disease and beriberi might be the same disease; but the absence of the classic signs in some cases of celiac disease made this conclusion unlikely.

DISCUSSION

DR. BELÁ SCHICK: We should be thankful to Dr. Haas for calling attention to the fact that certain cases of celiac disease show symptoms which are characteristic of beriberi. As Dr. Haas pointed out, other observers, with experience in celiac disease, realized the occurrence of symptoms indicating vitamin deficiency. Still found reports of four cases of scurvy in forty-one case reports that he

collected. I have seen a child with xerophthalmia in the course of the disease and another child with scurvy. I can confirm Dr. Haas' statement that children with celiac disease show weakness of the muscles, especially of those of the lower extremities. Some of the children are even unable to sit up; a change in the reflexes occurs, and edema is found in the face, in the lower extremities and in the hands. I, myself, had the impression that these cases resemble more closely the "hunger edema" than the beriberi which was seen in Europe as a consequence of the war. The "hunger edema" also shows, of course, symptoms of the different deficiency diseases. But I admit that the hydropic-atrophic form of beriberi shows similar symptoms.

The other forms of beriberi, the mild sensible-motoric form, the dry atrophic form and the pernicious acute form, do not come into the differential diagnosis.

Beriberi has been observed in Brazil. Lobelace saw 934 cases in four years. Beriberi was found by Little in Newfoundland, where white bread was eaten, and by Parkes in a prison in Elizabeth, New Jersey; by Reed among the Chinese and Japanese in California, and by Travis in Eddyville, Kentucky. Hoobler called attention to the possibility that mild forms of beriberi may occur more frequently even in this country than the public is aware.

According to McCarrison, dilatation of the stomach, enclosure of air within the intestinal tract and lack of control of the neurovascular apparatus of the gastrointestinal tract are characteristic of deficiency of vitamins.

By administering a deficient diet to monkeys, McCarrison was able to produce a picture similar to that of celiac disease, especially the peculiar white stools, which are so frequently seen in this disease and which are due, most likely, to the insufficient flow of the bile and the pancreatic juice. The stools were of normal color after the administration of vitamin extract, which stimulated the function of the liver and pancreas.

But if I understand rightly, Dr. Haas feels, as I do, that the vitamin deficiency is more likely a consequence of the celiac disease and its treatment than the cause of the disease.

For this reason I was always in favor of supplying the child suffering with celiac disease with what Wagner and I called "übungs diet" rather than with a "schönungs diet," and we restricted the treatment for the disease with protein milk and bananas to the period of acute symptoms. Fortunately, the deficiency of vitamins can be fought off with small quantities of foodstuffs rich in vitamins. Ibrahim and Feer and I, myself, advocate such a diet.

I agree with Dr. Haas that the difficulty in absorption of vitamins may frequently be more important than the absence of vitamins in the food.

DR. HAAS: I have nothing to add except that I cannot let this opportunity pass without restating my position with regard to the use of ripe bananas in celiac disease.

One of the cases illustrates their value. Although the symptoms of beriberi have all disappeared and the child has gained 27 pounds (12.2 Gm.) and grown 8 inches (32 cm.) in height in fourteen months, she cannot yet tolerate plain milk or other carbohydrates; this indicates that some condition other than the celiac disease existed.

To report as cured a child with celiac disease who has been on full diet for less than a year is really not adequate. Ripe bananas seem to have an amazingly stimulating effect on growth. The treatment for celiac disease with carbohydrate other than bananas illustrates this. The growth is usually not rapid, although the gain in weight may be great; but when bananas are given, the growth is satisfactory after a few months. Bananas contain all the vitamins except D, so that it is necessary to give cod liver oil in some form; however, plain cod liver oil is not tolerated in celiac disease. This difficulty may now be overcome by using cod liver oil concentrate-Metz or one of the activated preparations.

NATURAL HISTORY OF RHEUMATIC INFECTION; EVALUATION OF THERAPEUTIC MEASURES. DR. MAY G. WILSON.

Recent investigations concerning the etiologic rôle of streptococci in rheumatic infection (although not conclusive) have renewed interest in the use of serums and vaccines for therapeutic and prophylactic treatment.

The evaluation of these measures is dependent at the present time on a consideration of their influence on the clinical course of the disease. This is difficult in a disease which is so protean in its manifestations, apparently self limited in its acute stages and characterized by recurrences.

The contradictory results of various investigators as to the rôle of tonsillectomy in rheumatic infection are indicative of the need of some basic data on the natural history of this disease for comparative analysis.

I wish to present briefly some of the significant facts which were elicited from a statistical analysis of the case records of 413 children, covering a period from childhood through adolescence.

That rheumatic infection is a general infection is usually appreciated; nevertheless, some observers still view polyarthritis and chorea as clinical entities with heart disease as a complication.

An analysis of the clinical course of the disease in each child showed that the various manifestations, polyarthritis, growing pains and pains in the joints, chorea and carditis, occurred interchangeably and were not directly related to the duration of the disease or to the ultimate type or degree of involvement of the heart. While one is impressed with the chronicity of the disease, yet in my experience one, two, three, four or more years of freedom from symptoms of infection are not unusual. It is important here to indicate the need of a sufficiently long period of observation before evaluating prophylactic measures.

In considering the age of onset, it may be seen that beginning with the preschool age the curve gradually rises until the age of 6, remains high up to the age of 9 and then gradually declines. It would seem that prophylactic measures should be instituted before the age of 9.

Regardless of the particular type of manifestation, the initial sign of infection occurred in the age group comprising the years 6 to 9 (in about one half of the cases). It is to be noted that this was true except for tonsillitis which, as will be shown, presented an equal age distribution.

It was found that up to the age of 9 is the period of susceptibility and that at about 12 the tendency to infection begins to diminish, or one might say, immunity develops. It is obvious, then, that the results of any therapeutic measure instituted before or after children have reached the ages of 9 to 12 must be judged accordingly. The significance of this observation may be illustrated by a consideration of the influence of tonsillectomy.

A study of the average number of infections per child after the age specified for 245 children who were treated (tonsillectomy) and for 165 untreated (control) children showed a gradually diminishing number of infections after the age at which operation was performed. That this decline is not due to the favorable influence of tonsillectomy is seen from the fact that the curve for the control series runs parallel to it. For as indicated before, the period after the age of 9 is the period of developing immunity. As the age of the child increases, the average number of attacks a child may anticipate decreases.

It may be noted here that in view of the foregoing statement, the results of studies which include those of adults are therefore not comparable to those limited to children.

Tentative expectancy tables based on the experience of my associates and me with 413 children showed in general that at any age before 7 the chances were 3 to 5 that there would be a recurrence the following year. The chances were even between the ages of 7 and 11 and at any age after 12 the chances were 2 to 5, or less. Similarly, the number of consecutive years of freedom from infection tends to increase as adolescence is reached.

A consideration of the interval which elapsed between the first manifestation noted and the first recurrence showed that in one half of the cases relapses occurred within a year, in two-thirds in two years and in four-fifths in three years. The greatest incidence of recurrence within one year was observed in children who were first infected after the age of 10 (84 per cent were between the ages of 10 and 12). It is possible that this is a critical period for children with rheumatic infection.

Prevention of rheumatic heart disease is a much quoted statement, particularly in relation to therapy. Since 63 per cent of the children developed definite heart disease within one year of the onset and three-fourths in less than three years, it would seem more correct to speak of the prevention of rheumatic infection rather than the prevention of rheumatic heart disease.

It is obvious that an estimation of the value of prophylactic measures must be influenced by a consideration of the data presented. Similarly, evaluation of therapeutic measures instituted in the acute stages of rheumatic infection, i. e., polyarthritis, chorea and carditis, must take into consideration the variability of the manifestations in regard to duration and severity.

Small, using antistreptococcic serum, reported favorable results in a series of patients including some adults. An analysis of the case records published, particularly those of chorea, is not convincing.

The results in a small series of patients treated with Small's antiserum at the Rockefeller Institute and in the wards of the New York Nursery and Child's Hospital were not conclusive.

Several years ago, my associates and I used convalescent rheumatic fever serum in a small series of cases with apparently favorable, although not conclusive, results; similar results were obtained in a control series under routine treatment.

The drugs that at various times have been considered specific for chorea illustrate the variability in duration of this manifestation. It would seem that unless specific therapy was followed by striking improvement such as is observed following the use of diphtheria antitoxin, one must be cautious in evaluating the results of therapy instituted during periods of active infection. Furthermore, the treated patients should be controlled by a comparable group (untreated) of the same age constitution.

In view of the present interest in possible specific therapy, it is most important to have in mind the natural history of rheumatic infection as manifested in children.

DISCUSSION

DR. HOMER F. SWIFT: It is obvious that there was great need for just such a careful investigation as Dr. Wilson has carried out. I know of no place where similar work has been previously reported, and her study will serve as a model for other studies. It is a nucleus for increasing the knowledge of the life history of rheumatic fever in the young. In many respects, rheumatic fever in children differs from that in adults; certain of the manifestations, for example, arthritis, disappear quickly in children, whereas in adults arthritis runs a longer course, as a rule. In children, nodules occur much more frequently; chorea is encountered almost exclusively in children and adolescents. The need is therefore evident for a study of rheumatic fever in a large number of adults to complete these data of Dr. Wilson, and to determine the expectancy in later years of life. It is known, of course, that many adult patients receive antirheumatic treatment, and then return to their ordinary vocations without suffering afterward; but many of them, if kept under close observation, have mild relapses, mild attacks that do not compel the working man to give up his work but which indicate, nevertheless, the persistence of infection. Indeed, if adults who have had the disease are carefully observed one will find that many of them have mild manifestations of rheumatic fever over long periods. One class especially seems to harbor persistent infections, namely, the patients with mitral stenosis. I am sure that those who have been able to study these cases of mitral stenosis, particularly

in young women, must have been impressed with the chronicity of the infection in that group.

Dr. Wilson has not reported on the effect of tonsillectomy as extensively as she did in her recently published paper. It brings up the question of whether tonsillectomies should be performed as a routine. I should like to ask her whether in the group of nontonsillectomized children the disease was of as great severity as in those who were tonsillectomized. If two groups of patients are going to be compared, the condition in both groups should be of equal severity, if possible. In many of the studies reported, it seems probable that the patients who had had the tonsils removed, as a rule, had more severe types of rheumatic fever than did those in whom tonsillectomy had not been performed.

One point in the natural history of rheumatic fever would suggest that probably tonsillectomy was indicated. As is known, there exists a hypothesis of the etiology of rheumatic fever based, in part, on certain studies which show that in rabbits sensitization can be produced by making repeated foci of infection. This condition of hypersensitiveness, allergy, as it is called, is observed in the animals only after the production of foci with streptococci in contradistinction to intravenous inoculation and is kept up by continually making new foci in the animals. I have analyzed cases of rheumatic fever for years, and in the majority of them, particularly in adults, the acute attacks are preceded by tonsillitis in an antecedent period of between five weeks and from six to ten days. It seems to be the most common preceding disease. It seems justifiable, therefore, to think that tonsillitis may be the sensitizing "push," as it were, that moves the patient into a condition of allergy of sufficient intensity to bring on these manifestations. In the presence of multiple foci, the removal of one from an animal does not remove the condition of allergy or hypersensitiveness; it is no more reasonable to expect the elimination of one focus in the tonsil to eliminate the condition in the patient, if other foci are present; for if such is the case, the condition of hypersensitiveness will probably continue. In the past four or five years, my associates and I have been particularly struck with the fact that most of our patients who have had their tonsils removed and whose rheumatic infections continued were suffering from paranasal sinusitis. That is a point not sufficiently stressed, because attention is usually too closely focused on the tonsils. In some cases, sinusitis was so severe and extensive that operation was hardly justified. Dr. McCulloch has recently emphasized the point that paying attention to other parts of the upper respiratory tract has an important part in the treatment for these conditions. This does not in any way detract from Dr. Wilson's studies. It shows, however, that tonsillectomy is not enough and that other foci of infection must be regarded as of as much importance as those existing in the tonsils.

Dr. Wilson: In one third of the children, the tonsils were removed before the onset of any rheumatic manifestation; in about one-half, tonsillectomy was done within the first year of the onset. I should not say that the control series constituted a less susceptible group.

Appendicitis in Children. Dr. Charles E. Farr.

The appendix vermiformis is not unlike the pharyngeal tonsil in its reaction to infection or trauma. Both may and usually do return to a practically normal state even after repeated severe acute attacks. Observations during abdominal operations have repeatedly proved that the appendix is susceptible to even the slightest handling. Infectious processes similarly develop suddenly and frequently subside completely, leaving no trace. The appendix crippled by kinks, bands, etc., giving rise to the condition misnamed chronic appendicitis, is frequently so involved.

These crippled appendixes usually show symptoms, the chief of which are digestive disturbances. The differential diagnosis is by no means easy but can usually be attained by care in history taking, by skill in physical examination and by conservatism in interpretation of the laboratory data. Slight tenderness

and even slighter protective stiffening of the overlying rectus muscle are of immense diagnostic import. The rectal examination must never be omitted.

In competent hands, roentgen examination is of extreme importance. Failure to visualize the appendix, failure of it to empty in seventy-two hours, a fixed tender appendix or marked spasm of the pylorus with delayed emptying time must be given due weight in the diagnosis.

Children frequently suffer from abdominal lesions other than those of appendicitis. Many of these are amenable to surgical attack. A reasonably conservative attitude is correct, but operation offers little risk and will, if performed with skill and with fair indications, prevent many untimely deaths. Particularly in cases in the ward which cannot be followed with care, it is wiser to operate in the doubtful case than to run the risk of a disaster later on. By this means, the percentage of successful end-results is high.

In definite acute forms of the disease, it is permissible to operate through a buttonhole incision, if one wishes, but in the chronic type, an exploratory incision is preferable as by it other surgical lesions are frequently exposed and may be treated as indicated.

A survey has been made of all cases (805) of appendicitis in which treatment was given at St. Mary's Free Hospital for Children from 1903 to 1928, inclusive, and of those (654) on the First Surgical (Cornell) Division of the New York Hospital since 1915, a total of 1,459 cases. All were in children under 16 years of age.

There was a mortality of 75, or 5.2 per cent for the series, including both acute and chronic cases, or about 6 per cent for the acute type. The mortality in infants is high but drops rapidly during early childhood. After the age of 4, the death rate is even lower than it is in adults. Chronic cases have shown no mortality.

At the New York Hospital, there were no deaths in 243 consecutive acute cases in which the wounds were closed without drainage, i. e., early cases. Moreover, in 302 consecutive acute cases in which perforation did not occur, there were no deaths.

Although for the entire series the death rate is slightly higher than that in adults, it is felt that this is the result of delay in diagnosis and treatment. Particularly in children under 5 years of age, in whom the mortality rate in those with acute forms is about 13 per cent, delayed operation is the chief obstacle to better results. It is strongly urged that more intensive study in this age group would result in many operations in those with crippled or chronic appendixes and in those with early acute appendicitis. In this way, many lives would be saved.

DISCUSSION

DR. RICHARD W. BOLLING: The changes which Dr. Farr describes as occurring during manipulation of the normal appendix do take place, not only in the appendix but, under similar circumstances, in every part of the gastro-intestinal tract, and it had never occurred to me that they represented an acute inflammation. I agree that mild attacks of acute appendicitis occur frequently in young children and that many cases go unrecognized. It is only reasonable to assume this when the structure of the appendix at this time of life is considered, together with the fact that the rest of the intestinal tract is so liable to infection. The first five years of life is the period during which acute appendicitis is most important to the pediatrician. It is during this period that the mortality is so distressing. My personal experience in the age group of from 1 to 5 years comprises seventy cases with a mortality of 15, or over 20 per cent, more than twelve times the mortality in the age group from 6 to 15. More than 85 per cent of these children were admitted to the hospital with an abscess or a ruptured appendix and more or less widespread peritonitis. This condition is usually explained on the ground of the insidious onset, the rapid course of the disease and the great tendency of the appendix to rupture in young children, together with their lack of resistance. The duration of symptoms is interesting and has a bearing on the popular belief

that the course of appendicitis is much more rapid in children than in adults. In analyzing my series of cases, I find that the shortest duration of symptoms was twelve hours and the longest, three weeks. In only ten patients was the duration of symptoms before admission to the hospital less than two days, and all of these recovered. The average duration of symptoms before admission to the hospital was four and one-half days. It seems to me that one is inevitably led to the conclusion that the general conception of the clinical picture of acute appendicitis in young children is founded on a group of cases representing the last stages of the worst forms of appendicular inflammation. It is unreasonable to assume that an inflamed appendix in young children almost invariably tends to perforate. This impression has been derived from the fact that in those cases in which resolution takes place with more or less permanent damage to the appendix a diagnosis is usually not made until the occurrence of a subsequent attack at a time of life when the diagnosis is more easily made. There will continue to be many unnecessary deaths until it is firmly fixed in the minds of pediatricians that the high mortality in these young children is due chiefly to the inability to recognize the disease in its early stages and only to a small extent to whatever difference in clinical course and lack of bodily resistance is peculiar to this period of life.

Local tenderness is the most valuable of all signs. If this sign is accompanied by pain and vomiting with moderate elevation of temperature and leukocyte count, the diagnosis is reasonably sure. When I can convince myself that there is no local tenderness, I hesitate to make the diagnosis. While I believe that the statement that "the appendix is the abdominal tonsil" is better as a phrase than as an anatomic fact, I am inclined to think that it would be well if there were a therapeutic analogy between the tonsil and the appendix, and the custom became general of removing the appendix in young children on as slight grounds as those on which many tonsils are removed. Certainly the morbidity following the removal of an unruptured appendix is no greater, if as great, as that following the removal of a more or less normal tonsil. A well founded suspicion of appendicitis in an otherwise healthy child is an indication for removal of the appendix. In the older children, from 6 to 15 years of age, the pathologic condition and clinical course are similar to those in adults; the diagnosis is, if anything, easier and the operative results are at least as good. My own experience comprises 120 cases with 2 deaths, a mortality of less than half that in adults operated on under the same conditions.

The question of chronic appendicitis need be considered only exceptionally in younger children. In older children, in whom there have been recurring attacks of abdominal pain with nausea and vomiting and in whom the pain has been first referred to the epigastric region and later to the right lower quadrant together with some rise of temperature, the diagnosis is relatively clear and the indication for removal is obvious. When, however, the picture is one of obvious ill health without apparent cause and the symptoms and signs are referred rather indefinitely to the abdomen, the diagnosis is more difficult. In these circumstances, the appendix may fall under suspicion. Practically the only physical sign of importance is tenderness over the region of the appendix. In such cases it is usually by a process of elimination that a diagnosis is arrived at, and the diagnosis of chronic appendicitis is to be accepted only when every other possible cause for the symptoms has been excluded. I am inclined to be skeptical of the diagnosis of chronic appendicitis in children unless there is a history of one or more suggestive attacks. On the other hand, there are undoubtedly instances of an unsatisfactory state of health with vague abdominal symptoms in which there is an obvious improvement after removal of a chronically inflamed appendix.

I do not agree with Dr. Farr as to the method of procedure in cases in which the diagnosis of chronic appendicitis has been made after exhaustive clinical investigation. I believe that a general abdominal exploration should be made rarely and only in exceptional instances. The appendix should be approached directly, and with as little exposure of the viscera as possible. If symptoms

persist after such an operation, the question of general exploration may then be considered.

DR. CHARLES E. FARR: I believe with Dr. Bolling that early diagnosis and early operation will result in a great improvement in the mortality statistics. I also agree with him that the appendix in young children does not perforate and cause a suppurating peritonitis any earlier than in adults. Results will be as good or even better than in adults if there are more accurate observation and earlier operations.

Dr. Bolling and I differ slightly on the subject of chronic appendicitis, although even he agrees that the removal of the doubtful appendix is harmless and that in many instances it prevents grave trouble in the future. In spite of Dr. Bolling's views on the exploratory operation, I am still of the opinion that this is a beneficial procedure in infants and children just as it is in adults.

Book Reviews

LICHTWIRKUNG UND ANTIRACHITISCHER SCHUTLZSTOFF IM LEBENDEN ORGANISMUS. By CURT FALKENHEIM. Price, 9.80 marks. Berlin: S. Karger, 1928.

The book contains an excellent historical review of the investigations into the nature of the antirachitic vitamin and its relations to the action of light. Falkenheim's original work is described in detail. In his conclusions he seems to be torn between two disharmonious views on the pathogenesis of rickets. He is induced by his own experimental work to accept the view that rickets is a disease caused by growth in the presence of a deficiency in vitamin D and the ultraviolet waves of light between 290 and 313 microns. On the other hand, he wishes to retain the orthodox conception of manifold agencies, among them, disposition. His experiments which deal with the latter subject show nothing more than that vitamin D can be increased in the mother's milk by irradiating the nursing mother. Falkenheim's most serious error is his underestimation of the importance of rapid growth. This is particularly distressing when he ascribes the early and serious rickets of prematures to a peculiar "disposition," an acidosis of the premature infant, decreased vitamin D depot, etc.

The publication does, however, contain a wealth of information and will prove interesting and instructive to the reader who is armed against the aforementioned errors. Particularly interesting are Falkenheim's experiments which indicate that localized irradiation of the back of rats increases the supply of vitamin D in the unirradiated areas of the skin. The author assumes that this is due to transport from the irradiated portion. This skin acts as an antirachitic factor in the rickets of rats whether it is given by mouth or parenterally by implantation in a subcutaneous skin pouch. The extirpation of the spleen does not influence the development or healing of rickets in rats. Milk obtained from cows which had been kept by an experimental station in open pasture during the entire summer showed only a small and uncertain antirachitic value. Vitamin D is well preserved in milk obtained from irradiated cows and Falkenheim succeeded in demonstrating its relative stability during a period of five and one-half months in milk that had been treated with carbon dioxide, pasteurized and then iced. Cow's milk that heals rickets in rats, in doses of less than 5 cc. daily, is probably without influence on rickets in human beings.

NÄHRSCHÄDEN DES KINDES. PROF. HANS ARON. Price, 6 marks. Pp. 152, with 37 illustrations. Vienna: Urban & Schwarzenberg, 1928.

The author has attempted to gather and coordinate the points of view of European writers on the subject of disturbances of nutrition in infants under 3 years of age. His technic is not the usual. He begins with a definition of Nährschäden (disturbances of nutrition) that apparently covers the subject: "Manifestations of illness that can be relieved by proper changes in the feeding are disturbances of nutrition."

A classification is essential to the development of the subject, and the author bases his classification on the etiology, modifying it by showing that no case will be found that is limited purely to one group. For discussion the disturbances are divided into those of the breast-fed and those of the artifically-fed infants. The first group under the breast-fed is given as acute and chronic inanition. He suggests irradiation with quartz light as a possible galactagogue.

Considering the disturbances of nutrition of the artificially-fed infants, he states the truism that it is impossible to feed all children according to a definite scheme. Then follows the discussion of insufficient food, quantitatively and qualitatively, excess food and the gradual development of severe chronic nutritional disturbances from these. He takes up the nutritional disturbances due to qualitative insufficiency under separate heads as: insufficient and excess protein, insufficient and excess carbohydrate and insufficient and excess fat. The last fifty pages of the booklet are devoted to the illnesses arising from insufficient vitamins, that is, avitaminosis.

All the recent feeding preparations are described, and numerous histories fully illustrative of the form of disturbance under discussion are cited. This is a worthy work and seems to call for a similar work reviewing the present treatments in vogue in this country.

ERGEBNISSE DER LIPOIDSTOFFWECHSELFORSCHUNG MIT BESONDERER BERÜCKSICHTINGUNG DER VERHÄLTNISSE IM KINDESALTER. By DR. HANS KNAUER. Price, 7 marks. Pp. 164. Berlin: S. Karger, 1928.

This monograph on the lipoids contains a full discussion of the chemistry and metabolism of both the fats and the lipoids. The biologic properties of these substances and the rôle in animal and plant life are discussed. The variations in the lipoids of the blood in a variety of pathologic conditions are considered, including nutritional disturbances, blood diseases and diseases of the endocrine glands, including pancreatic diabetes. The influence of infections, light therapy and various poisons on the lipoid metabolism is mentioned. Present knowledge concerning the lipoid content of the stools, urine, cerebrospinal fluid and glandular secretions is summarized. The monograph concludes with the discussion of the synthesis and breakdown of the lipoids in the animal body.

Especially valuable are the references to the literature, numbering in all something like 500. These references are complete so far as the German literature is concerned, although some of the more recent French and American references are not cited. The monograph, as a whole, presents in abstract form present knowledge concerning the lipoids. There is not a great deal of detailed discussion, but with the complete references to the literature, information concerning details may be readily obtained. The book suffers from lack of an index.

WHAT EVERY ONE SHOULD KNOW ABOUT EYES. F. PARK LEWIS. Price, 30 cents. Pp. 70, with 7 illustrations. New York: Funk & Wagnalls Company, 1928.

This interesting little book contains just what its name implies. The first part is a short résumé of the mechanism of sight, the physics of the eye, how the eyes are tested, the cause of nearsightedness and cross-eye, the way glasses are fitted and something as to when they should be used and when not used. The second part takes up some of the more common diseases of the eye such as pink-eye and trachoma. Birth infections, congenital syphilis and accidents and injuries are also discussed. The third part gives the changes that are found in middle life, and the results of age are dealt with, particularly cataract and glaucoma. The book ends with a discussion of the disabilities that are inheritable, such as congenital cataract and color blindness.

One of the most interesting parts of the book deals with the problem that is concerning the world at present, namely, the subject of throwing away one's glasses. This the author treats as a fad. The human race for many years existed without the use of glasses, but that was back in the dark ages, and return to the glassless age would be a return to the dark ages. Glasses should not be worn except when they are beneficial, but when they are of benefit they should not be dispensed with. The book is very readable, and only seventy pages long.

THE INFANT AND YOUNG CHILD—ITS CARE AND FEEDING FROM BIRTH UNTIL SCHOOL AGE—A MANUAL FOR MOTHERS. By DR. LEWIS WEBB HILL, DR. JOHN LOVETT MORSE and DR. EDWIN T. WYMAN. Second edition. Price, $2. Pp. 299, with illustrations. Philadelphia: W. B. Saunders Company, 1929.

This second edition of a book for popular use contains about 300 pages and a few illustrations. It deals with useful information for the mother regarding the clothing, hygiene, details of feeding, evidences of indigestion in the artificially-fed, feeding in older children and methods of preparing foods for later childhood. No attempt is made to tell the mother how to devise her own formulas for feeding the infant. The latter third of the book deals with the development, environment, training and common diseases of childhood. This is a perfectly safe and sane book which any physician can well recommend to his clientele.

Directory of Pediatric Societies

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SECTION ON DISEASES OF CHILDREN

Chairman: Dr. W. A. Mulherin, 753 Broad St., Augusta, Ga.
Secretary: Dr. C. A. Aldrich, 545 Lincoln Ave., Winnetka, Ill.
Place: Portland, Ore. Time: July 8-12, 1929.

AMERICAN PEDIATRIC SOCIETY

President: Dr. Henry L. K. Shaw, 142 Washington Ave., Albany, N. Y.
Secretary: Dr. Howard Childs Carpenter, 1805 Spruce St., Philadelphia.
Place: St. Louis. Time: May 20-22, 1929.

THE ASSOCIATION OF AMERICAN TEACHERS OF THE DISEASES OF CHILDREN

President: Dr. Paul W. Emerson, 86 Bay State Road, Boston.
Secretary: Dr. Ralph M. Tyson, 1527 Pine St., Philadelphia.
Place: Portland, Ore. Time: July 8-12, 1929.

AMERICAN CHILD HEALTH ASSOCIATION

President: Hon. Herbert Hoover, 370 7th Ave., New York.
Secretary: Dr. Philip Van Ingen, 370 7th Ave., New York.
Place: Minneapolis. Time: Sept. 30-Oct. 4, 1929.

CANADIAN SOCIETY FOR THE STUDY OF DISEASES OF CHILDREN

President: Dr. Thomas Crossan Clark, 51 Herkimer St., Hamilton, Ont.
Secretary-Treasurer: Dr. Frank H. Boone, 164 James St. S., Hamilton, Ont.

SECTIONAL

CENTRAL STATES PEDIATRIC SOCIETY

President: Dr. J. Gurney Taylor, 120 E. Wisconsin St., Milwaukee.
Secretary: Dr. A. H. Parmelee, 310 S. Michigan Ave., Chicago.
Place: Milwaukee. Time: October, 1929.

SECTION ON PEDIATRICS OF SOUTHERN MEDICAL ASSOCIATION

Chairman: Dr. J. H. Eugene Rosamond, 1074 Madison Ave., Memphis, Tenn.
Secretary: Dr. A. J. Waring, De Renne Apts., Savannah, Ga.
Place: Miami, Fla. Time: Nov. 20-22, 1929.

LOCAL

ALABAMA PEDIATRIC SOCIETY

President: Dr. J. MacBell, Mobile.
Secretary-Treasurer: Dr. Hughes Kennedy, Jr., Highland Plaza Apts., Birmingham.

NORTHERN CALIFORNIA PEDIATRIC SOCIETY

President: Dr. W. L. Channell, Medical Bldg., Oakland.
Secretary: Dr. J. E. Parrott, Medico-Dental Bldg., San Francisco.
Place: Various Teaching Schools. Time: Monthly.

SOUTHWESTERN PEDIATRIC SOCIETY

President: Dr. Ezra S. Fish, 523 W. 6th St., Los Angeles.
Secretary: Dr. Fred L. Glascock, 1136 W. 6th St., Los Angeles.
Place: University Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

THE ROCKY MOUNTAIN PEDIATRIC SOCIETY

President: Dr. Elsie Seelye Pratt, Republic Bldg., Denver.
Secretary and Treasurer: Dr. Wilford W. Barber, Metropolitan Bldg., Denver.
Place: Children's Hospital, Denver. Time: Third Saturday of each month, 2:30 p. m., September to May, inclusive.

GEORGIA PEDIATRIC SOCIETY

President: Dr. W. N. Adkins, Medical Arts Bldg., Atlanta.
Secretary and Treasurer: Dr. E. N. Gleaton, 212 E. Gaston St., Savannah.

PEDIATRIC SECTION OF FULTON COUNTY MEDICAL SOCIETY, ATLANTA, GA.

Chairman: Dr. Lee Bivings, Exchange Bldg., Atlanta.
Secretary: Dr. William Kiser, Medical Arts Bldg., Atlanta.
Place: Academy of Medicine, 32 Howard St., Atlanta. Time: Second Thursday of each month from October to April, at 8 p. m.

NEW ENGLAND PEDIATRIC SOCIETY

President: Dr. Edwin T. Wyman, 483 Beacon St., Boston.
Secretary-Treasurer: Dr. Randolph K. Byers, 66 Commonwealth Ave., Boston.
Place: Boston Medical Library. Time: Second Friday of each month.

CHICAGO PEDIATRIC SOCIETY

President: Dr. Maurice Blatt, 185 N. Wabash Ave., Chicago.
Secretary: Dr. J. K. Calvin, 104 S. Michigan Ave., Chicago.
Place: City Club. Time: Third Tuesday of each month.

LOUISIANA STATE PEDIATRIC SOCIETY

President: Dr. L. R. De Buys, 1417 Delachaise St., New Orleans.
Secretary-Treasurer: Dr. C. T. Williams, 7401 Burthe St., New Orleans.

DETROIT PEDIATRIC SOCIETY

President: Dr. M. Boyd Kay, 10 Peterboro St., Detroit.
Secretary: Dr. Charles A. Wilson, 71 E. Ferry St., Detroit.
Place: Children's Hospital of Michigan. Time: No fixed date; approximately once a month.

NORTHWESTERN PEDIATRIC SOCIETY

President: Dr. C. R. Moriarity, La Salle Bldg., Minneapolis.
Secretary: Dr. E. S. Platou, 730 La Salle Bldg., Minneapolis.
Place: University Campus and Rochester, Minn. Time: Winter, Spring, Summer, Fall.

ST. LOUIS PEDIATRIC SOCIETY

President: Dr. Park J. White, Beaumont Bldg., St. Louis.
Secretary-Treasurer: Dr. Ralph L. Cook, 508 N. Grand Blvd., St. Louis.
Place: St. Louis Children's Hospital. Time: At least once a year and contingent thereafter on the arrangement of a suitable program.

NEBRASKA-IOWA PEDIATRIC SOCIETY

President: Dr. Floyd Clarke, City Nat'l Bank Bldg., Omaha.
Secretary: Dr. R. B. Eldredge, Medical Arts Bldg., Omaha.
Place: Add-Sell Restaurant. Time: Second Thursday of each month from October to May, inclusive, 6 p. m.

BROOKLYN PEDIATRIC SOCIETY

President: Dr. Louis M. Ruderman, 961 Eastern Parkway, Brooklyn.
Secretary: Dr. Joseph F. Paulonis, 1357 Bushwick Ave., Brooklyn.
Place: Kings County Medical Society Bldg. Time: Last Wednesday of each month, except June, July and August.

BRONX PEDIATRIC SOCIETY

President: Dr. L. H. Barenberg, 1749 Grand Concourse, New York.
Secretary: Dr. Joseph Golomb, 496 E. 175th St., New York.
Place: Concourse Plaza, 161st St. and Grand Concourse, New York. Time: Second Wednesday of each month, except June, July, August and September.

CENTRAL NEW YORK PEDIATRIC CLUB

President: Dr. Frank Vander Bogert, 111 Union St., Schenectady.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Place: Various cities in New York. Time: Fourth Thursday of October, January and April.

NEW YORK ACADEMY OF MEDICINE, SECTION OF PEDIATRICS

President: Dr. Stafford McLean, 17 E. 71st St., New York.
Secretary: Dr. F. Elmer Johnson, 300 West End Ave., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

ROCHESTER PEDIATRIC SOCIETY

President: Dr. Paul W. Beaven, 26 S. Goodman St., Rochester, N. Y.
Secretary: Dr. Edwin R. Reynolds, 1620 St. Paul St., Rochester, N. Y.
Place: Arranged by program committee. Time: First Friday of each month from October to May.

ACADEMY OF MEDICINE OF CLEVELAND, PEDIATRIC SECTION

Chairman: Dr. C. W. Wyckoff, 8314 Euclid Ave., Cleveland.
Secretary: Dr. C. L. Ruggles, 10616 Euclid Ave., Cleveland.
Place: 2009 Adelbert Road. Time: Four meetings, from September to May.

PHILADELPHIA PEDIATRIC SOCIETY

President: Dr. Ralph M. Tyson, 334 S. 21st St., Philadelphia.
Secretary: Dr. John D. Donnelly, 115 Bryn Mawr Ave., Bala-Cynwyd, Pa.
Place: College of Physicians, 19 S. 22d St., Philadelphia. Time: Second Tuesday of each month from October to June, inclusive.

PITTSBURGH PEDIATRIC SOCIETY

President: Dr. Zaccheus R. Scott, Westinghouse Bldg., Pittsburgh.
Secretary: Dr. Theodore C. Elterich, Highland Bldg., Pittsburgh.
Place: Pittsburgh Academy of Medicine. Time: Second Friday, alternate months.

THE SOUTH CAROLINA PEDIATRIC SOCIETY

President: Dr. E. A. Hines, Seneca.
Secretary-Treasurer: Dr. R. M. Pollitzer, 105 E. North St., Greenville.
Place: Charleston. Time: May 8, 1929.

MEMPHIS PEDIATRIC SOCIETY

President: Dr. A. G. Quinn, 1193 Madison Ave., Memphis, Tenn.
Secretary: Dr. Kinsey M. Buck, 1024 Madison Ave., Memphis, Tenn.
Place: Memphis General Hospital. Time: Second Tuesday of each month.

TEXAS PEDIATRIC SOCIETY

President: Dr. Edwin G. Schwarz, Medical Arts Bldg., Fort Worth.
Secretary-Treasurer: Dr. Ramsey Moore, Medical Arts Bldg., Dallas.

RICHMOND PEDIATRIC SOCIETY

President: Dr. J. B. Stone, 2042 Park Ave., Medical Arts Bldg., Richmond, Va.
Secretary-Treasurer: Dr. Samuel A. Anderson, Jr., 2326 W. Grace St., Richmond, Va.
Place: Westmoreland Club, 601 E. Grace St., Richmond, Va. Time: First Thursday of each month (other than during the summer).

VIRGINIA PEDIATRIC SOCIETY

President: Dr. Charles E. Conrad, Harrisonburg.
Secretary: Dr. William B. McIlwaine, Petersburg.

NORTH PACIFIC PEDIATRIC SOCIETY

President: Dr. E. D. Carder, 736 Granville St., Vancouver, B. C.
Secretary and Treasurer: Dr. George A. Lamont, 736 Granville St., Vancouver, B. C.

SEATTLE PEDIATRIC SOCIETY

President: Dr. Arthur H. Gray, Lumber Exchange Bldg., Seattle.
Secretary: Dr. Armin Rembe, Stimson Bldg., Seattle.
Place: College Club. Time: Third Friday of each month, at 7 p. m.

MILWAUKEE PEDIATRIC SOCIETY

President: Dr. A. L. Kastner, 120 E. Wisconsin St., Milwaukee.
Secretary: Dr. F. R. Janney, 418 E. North Ave., Milwaukee.
Place: Children's Hospital, Milwaukee. Time: Second Wednesday of each alternate month, beginning with February.

ACADEMY OF MEDICINE, TORONTO, SECTION OF PEDIATRICS

President: Dr. G. A. Davis, 12 Belsize Dr., Toronto.
Secretary: Dr. Gladys Boyd, 56 DeLisle St., Toronto.
Time: November 17, December 15, February 16 and March 15.